


 Cite this: *RSC Adv.*, 2025, 15, 37125

A review on the sulfur ylide-mediated Corey–Chaykovsky reaction: a powerful approach to natural product synthesis

 Ammara,^a Asim Mansha,^a Samreen Gul Khan,^a Ameer Fawad Zahoor,^a Muhammad Jawwad Saif,^b Bushra Parveen,^a Muhammad Athar Saeed,^c Aijaz Rasool Chaudhry,^d Ahmad Irfan^e and Muhammad Abbas^d

 Received 10th July 2025
 Accepted 4th September 2025

DOI: 10.1039/d5ra04921k

rsc.li/rsc-advances

The Corey–Chaykovsky reaction is an efficient transformation in organic syntheses, which enables the construction of 3-membered cores *via* a sulfur ylide-mediated process. The reaction enables a simple yet versatile strategy to access cyclopropanes, epoxides and aziridines. The resulting cyclic frameworks are significantly valuable for the synthesis of several structurally complex compounds, including numerous natural products and their analogues. This review underscores the importance and utility of the Corey–Chaykovsky reaction towards the total synthesis of several classes of natural products reported since 2020.

1 Introduction

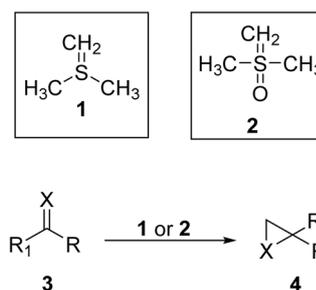
C–C bond-forming reactions are ubiquitously employed in organic transformations to carry out chain elongation and functionalization.^{1–3} In organic synthesis, the Corey–Chaykovsky reaction (CCR), introduced by Corey and Chaykovsky in 1960, is a significant carbon–carbon bond-forming reaction that deals with the efficacious synthesis of aziridine, cyclopropane and epoxide through the reaction of respective functionalized olefinic compounds with dimethylsulfonium methylide **1** or Corey's ylide (dimethylsulfoxonium methylide) **2** (Scheme 1). The functionalized olefinic compound may include imine, carbonyl, enones or thiocarbonyl.^{4–7}

In the classic Corey–Chaykovsky reaction, the deprotonation of sulfoxonium and sulfonium halides generates ylides in the presence of a strong base, and the resulting ylides react with ketones/aldehydes and enones to yield oxirane and cyclopropylketones, respectively. The typically used bases are NaH, *t*BuOK and BuLi, with THF, dioxane and DMF employed as solvents.^{1,8–14}

Johnson and colleagues first documented the mechanism for the CCR using a carbonyl group and sulfonium ylide, which has received acceptance from the scientific community. Sulfoxonium ylide **5** nucleophilically attacks the electrophilic center of **6** to form a zwitterionic intermediate, **A**. The intermediate **A**

yields a 3-membered ring **8**, facilitated by an intramolecular S_N2 reaction, where X is the nucleophile and sulfide is the leaving group (Fig. 1). For all other sulfide derivatives, the same mechanism may be employed. The sulfonium ylide, being more reactive, reacts with deactivated ketones, whereas the oxosulfonium ylide remains inert. Upon reaction *via* α–β unsaturated ketones, oxosulfonium selectively adds to the olefinic bond, whereas sulfonium ylide may generate oxirane or cyclopropane depending on the substituent (Fig. 1).^{15–17}

Since the discovery of the Corey–Chaykovsky reaction, various research groups have employed several methodological modifications to carry out the facile synthesis of targeted



Scheme 1 General representation of the Corey–Chaykovsky reaction.

^aDepartment of Chemistry, Government College University Faisalabad, 38000-Faisalabad, Pakistan. E-mail: fawad.zahoor@gcuf.edu.pk

^bDepartment of Applied Chemistry, Government College University Faisalabad, 38000-Faisalabad, Pakistan

^cDepartment of Chemistry and Biochemistry, Auburn University, 36849 Alabama, USA

^dDepartment of Physics, College of Science, University of Bisha, P. O. Box 551, Bisha 61922, Saudi Arabia

^eDepartment of Chemistry, College of Science, King Khalid University, P. O. Box 9004, Abha 61413, Saudi Arabia

^fDepartment of Chemistry, Forman Christian College University, 54600, Lahore, Pakistan. E-mail: muhammadabbas@fccollege.edu.pk



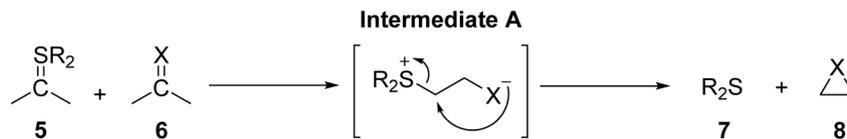


Fig. 1 General mechanism for the Corey–Chaykovsky reaction.

molecules to address challenges such as the stereo-control, structural complexity and chemoselectivity of the reactions with α , β -unsaturated ketones. The recent methodological development of the Corey–Chaykovsky reaction includes the following: the fluoromethyl sulfonium reagent for the synthesis of fluorocyclopropane derivatives,¹⁸ Amberlyst-A26 (ref. 19) as the base for direct cyclopropanation, and a metal-free approach involving ILs²⁰ as the catalyst and solvent. These innovations provide a valuable alternative to classical methods, enhancing the scope and versatility of the reaction.

Several heterocyclic scaffolds are of significant interest in medicinal and synthetic chemistry owing to their vast biological activities.^{22–24} The CCR proceeds *via* the introduction of sulfur ylide to electrophiles (enones, carbonyls, imines), serving as an essential tool in the formation of three-membered rings (cyclopropane, epoxide and aziridine) and a variety of different compounds.^{25,26} Owing to the easy handling and affordability of the reactants, the CCR is a robust technique for cyclopropane synthesis. It has gained prominence over the past decade due to the significant advancement of donor–acceptor cyclopropane chemistry.^{27–30} Cyclopropanes are ubiquitous moieties with versatile effects in agrochemicals and pharmaceuticals.³¹ Several biologically active natural products have also been found to include a cyclopropane ring in their structural frameworks.^{32–35}

The Johnson–Corey–Chaykovsky epoxidation is a pioneering synthesis technique for a structurally versatile class of terminal oxiranes.³⁶ The asymmetric version of CCR (*via* a chiral sulfide) has been developed over the past thirty years to complement alkene epoxidation.^{7,37–41} The *retro*-Corey–Chaykovsky epoxidation involves the efficient transformation of epoxides to ketones in a non-oxidative and mildly basic environment.⁴² The aza-Corey–Chaykovsky reaction was first reported by Aggarwal *et al.* as an efficacious carbenoid-addition approach to attain aziridines.^{43,44} The modification in traditional aza-CCR not only addresses the limitations in ketimine aziridination but also provides a practical route for the development of complex amino acid derivatives, reinforcing the versatility of Corey's original approach in modern synthetic strategies.⁴⁵

The synthesis of natural products has always been a challenging and interesting subject for synthetic researchers.^{46–49} The CCR provides a simple yet versatile strategy to convert any ethylenic moiety and, further, to develop natural products and structurally complex compounds.^{50–52} E. J. Corey and his research group developed many new synthetic substances with intricate organic frameworks. They also carried out the total synthesis of significant natural compounds that encouraged the development of organic syntheses in recent years.⁵³ The Corey–Chaykovsky reaction has been found to be involved in the generation of a variety of lactones,⁵⁴ heterocyclic compounds,⁵⁵ and functionalized furans⁵⁶ as well as in the remodeling of

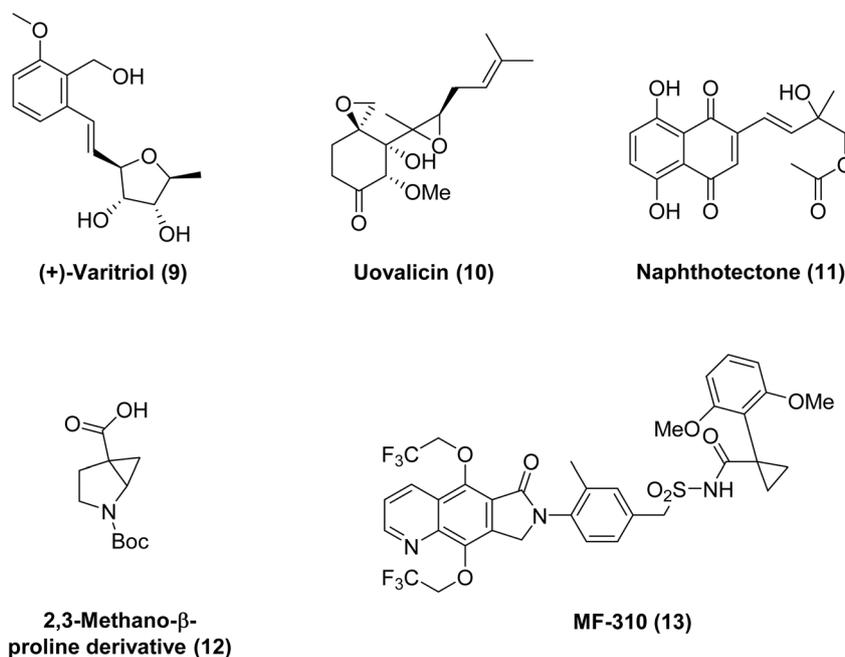


Fig. 2 Structures of natural products formed by employing the CCR as a key step.



pyridium salts.⁵⁷ The asymmetric CC cyclopropanation⁵⁸ also finds its applications towards the synthesis of dihydrofurans and several new classes of hydrofluorenones.⁵⁹ In addition, asymmetrical intramolecular CC epoxidation has been reported to obtain vepdegestrant.⁶⁰ Till now, various natural products and synthetic analogs of natural products (aza-cryptophycin)⁶¹ have been synthesized by incorporating the CCR as one of the significant steps, thereby highlighting its importance. Some of these bioactive natural products, such as (+)-varitriol **9**,⁶² uovalicin **10**,⁶³ naphthotectone **11**,⁶⁴ 2,3-methano- β -proline derivative **12** (ref. 65) and MF-310 **13** (ref. 66) have been successfully synthesized by the CCR, whose structures are displayed in Fig. 2.

Altogether, the chemically stable and economical sulfur ylide reagents, regio and stereoselectivity, wide substrate scope, mild conditions, good yields and metal-free approach demonstrate the noteworthiness of the CCR for synthesizing various natural products. To date, only two reviews have been published featuring the applications of the CC cyclopropanation⁶⁷ and the methodological developments of the CCR, along with the total synthesis of natural products.⁶⁰ The purpose of our review is to highlight the recent applications of the Corey–Chaykovsky reaction as a pivotal step to access the diverse range of natural products reported since 2020.

2 Literature review

2.1. Synthesis of alkaloid-based natural products

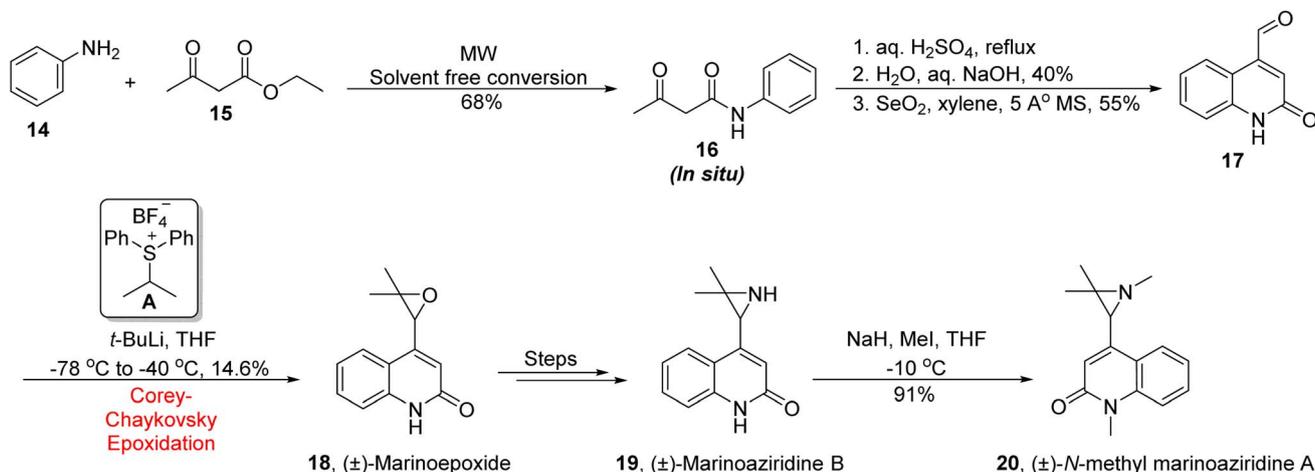
The structures of two novel marine-derived chiral alkaloids, *i.e.*, marinoaziridine A and B, were isolated from the marine Gram-negative bacteria (Cytophagales order).⁶⁸ Marinoaziridines not only possess the therapeutically interesting quinolin-2(1*H*)-one ring but also the aziridine rings^{69–71} featuring one stereocenter, allowing two enantiomers of each product. Both enantiomers are capable of exhibiting selective and distinct bioactivity.

In 2024, Buljan *et al.*⁷² reported the total synthesis of (\pm)-marinoaziridine B **19**, which involved the Staudinger reaction and the Johnson–Corey–Chaykovsky epoxidation as key

steps.⁷³ Attempts to synthesize (\pm)-marinoaziridine A have not been successful so far, yielding only its (\pm)-*N*-methyl derivative **20**. Buljan and coworkers explored the synthetic pathway involving the reaction of aniline **14** with ethyl acetoacetate **15** *via* microwave irradiation to furnish compound **16** in 68% yield, which in turn was subjected to the Knorr reaction, followed by Riley's oxidation⁷⁴ to accomplish aldehyde **17** in 55% yield. Moving forward, the Corey–Chaykovsky reaction between aldehyde **17**, sulfonium salt A (obtained by an AgBF₄-mediated reaction between 2-iodopropane and dimethyl sulfide⁷⁵) and the *in situ* base-generated sulfur ylide, utilizing *t*-BuLi as the base in tetrahydrofuran, produced (\pm)-marinoepoxide **18** (at -78 °C to -40 °C) in 14.6% yield.⁷³ Consequently, the epoxide **18** was subjected to a multiple-step process to generate (\pm)-marinoaziridine B **19** in 80% yield, which was transformed into (\pm)-*N*-methyl marinoaziridine A **20** in 91% yield by utilizing MeI reagent and sodium hydride as the base (Scheme 2).

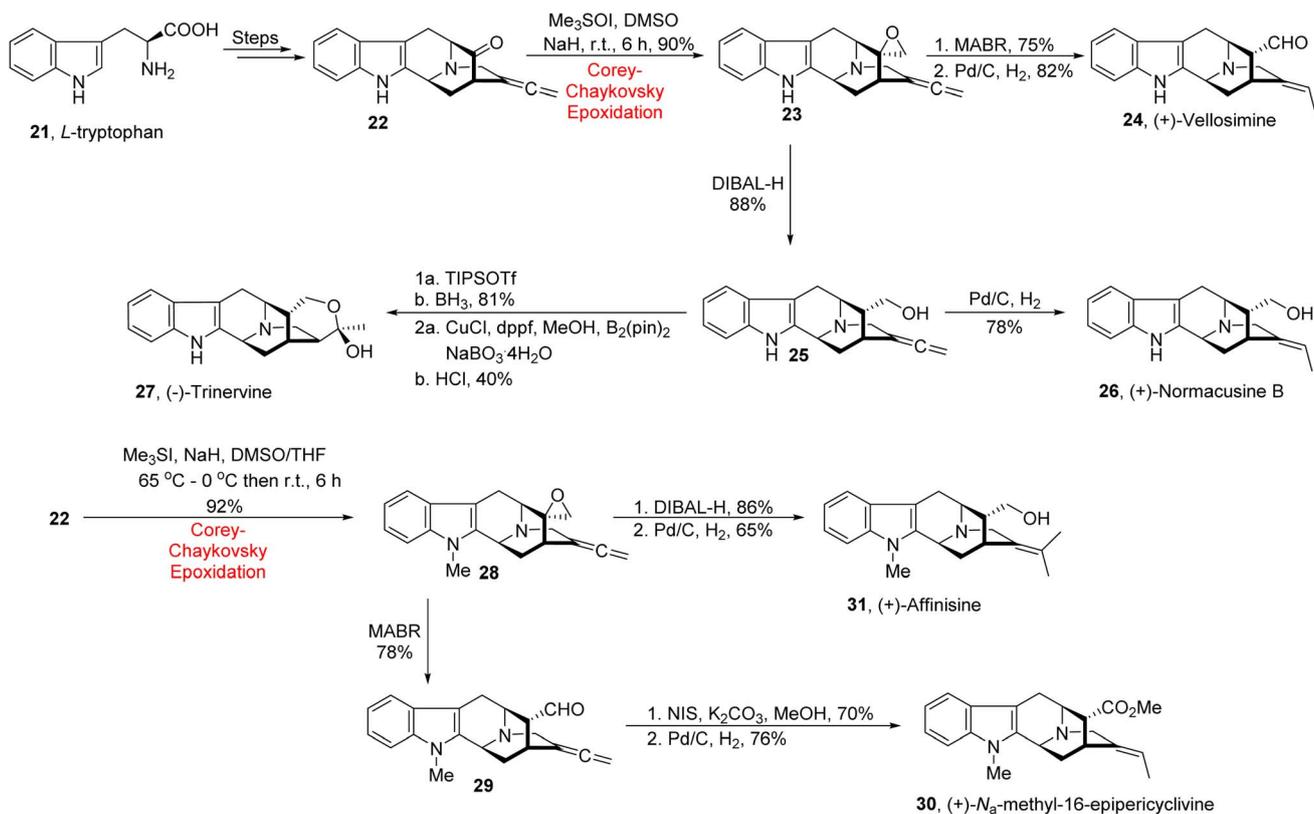
Sarpagine alkaloids are members of the monoterpene indole alkaloid family, mainly isolated from plant families (Apocynaceae and Gelsemiaceae).^{76–80} Structurally, they are characterized by a cage-shaped core framework, involving indole-fused azabicyclo[2.2.2]octane and azabicyclo[3.3.1]nonane as substructures. Ajmaline, a notable analog of sarpagine alkaloid, is diagnostically used for Brugada syndrome.⁸¹ Koumine alkaloids, originating from sarpagine alkaloids,^{82,83} exhibit a wide range of analgesic, anti-tumor, immunomodulatory and anti-inflammatory properties.^{84,85} However, the putative bioactivities of sarpagine alkaloids are yet to be explored, presumably because of their scarce nature.

In 2021, Yang *et al.*⁸⁶ strategically developed a unified total synthetic pathway for both Koumine and Sarpagine alkaloids, utilizing the Corey–Chaykovsky reaction as one of the key steps. Their strategy involved using *L*-tryptophan **21** (ref. 87) as a starting material for the construction of cage intermediate **22** in a multiple-step process, featuring allene and ketone groups. The assembly of a cage scaffold of intermediate **22** involves two structural transformations: (a) formation of the bicyclo[2.2.2]octane core *via* ketone α -allylation and (b) construction of the



Scheme 2 Synthesis of (\pm)-marinoaziridine B **19**.





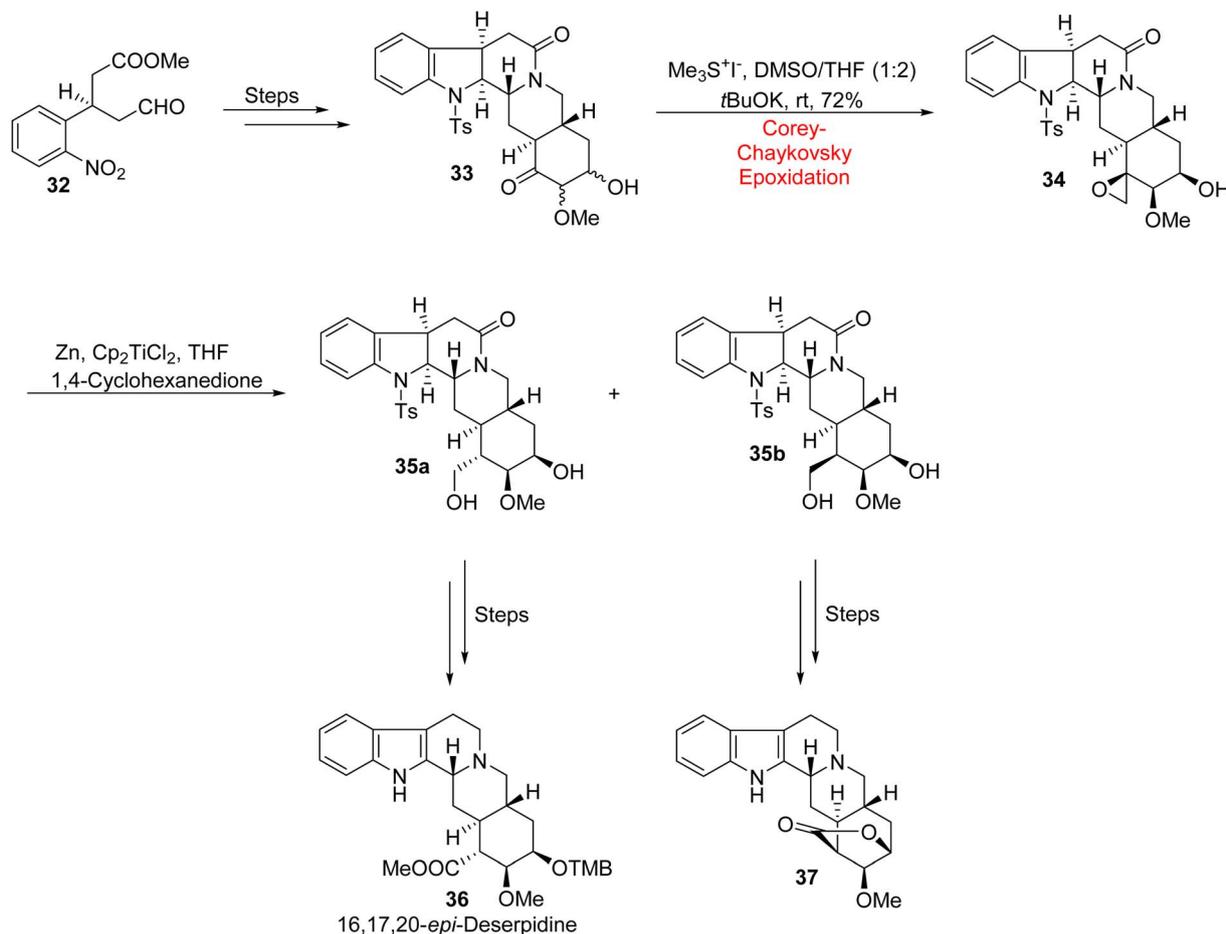
Scheme 3 Synthesis of sarpagine alkaloids.

bicyclo[3.3.1]nonane core through intramolecular oxidative cyclopropanol cyclization. Their strategy enabled the synthesis of a wide range of sarpagine alkaloids with different substituents after accessing the key precursor **22**. The intermediate **22** was subjected to the Corey–Chaykovsky reaction in the presence of Me_3SOI and sodium hydride in DMSO at room temperature for 6 hours to obtain epoxide **23** in 90% yield. Upon the treatment of epoxide **23** with MABR (methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide)), followed by partial allene hydrogenation, (+)-vellosimine **24** was afforded in good yield (>20 : 1 *E/Z* selectivities). Conversely, epoxide **23** was transformed into alcohol **25** (88%) by treating it with DIBAL-H, which was further converted into (+)-normacusine B **26** (>20 : 1 *E/Z*) by partial allene hydrogenation. However, the protection of the hydroxyl group and nitrogen atom of alcohol **25** as a borane-complexed silyl ether, the oxidation/hydrogenation of the allene moiety using Ma's protocol,⁸⁸ and silyl group deprotection and borane removal led to the preparation of (–)-trinervine **27** in 40% yield. Next, the Corey–Chaykovsky reaction of intermediate **22** with Me_3SI ylide, NaH in DMSO/THF (at 65°C to 0°C , then at rt, 6 h) afforded epoxide **28** in 92% yield, along with the addition of the –Me group on the indole nitrogen. Treating compound **28** with MABR produced compound **29** in 78% yield, which was further subjected to halogenation and partial hydrogenation to achieve (+)- N_a -methyl-16-epipericyclivine **30** in 76% yield.⁸⁹ Conversely, the reduction of **28** followed by partial hydrogenation afforded (+)-affinisine **31** in 65% yield (Scheme 3).

Reserpine and its congener deserpidine are significant Rauwolfia alkaloids that were extracted in the 1950s.^{90–92} They have the potential to exhibit sedative and anti-hypertensive activities.⁹³ Both molecules are composed of a yohimbine scaffold and a highly functionalized cyclohexane ring; thus, the construction of these molecules poses a significant synthetic challenge. The total synthesis of naturally occurring deserpidine has rarely been reported compared to the case with reserpine,^{94–99} and the only available asymmetric strategy involves the conversion of reserpines to deserpidine.⁹⁹ Wu and co-workers⁹⁹ accomplished the first asymmetric total synthesis of a stereoisomer of deserpidine in 2021 by employing a visible-light-induced radical cascade strategy¹⁰⁰ involving the Corey–Chaykovsky reaction as a significant step. To synthesize the deserpidine with a complete corynanthe scaffold, they aimed to assemble the tetracyclic ring system through the inter/intramolecular radical cascade reaction, which proceeded by ring formation.

The synthetic endeavor towards the total synthesis of deserpidine was commenced with the preparation of pentacyclic compound **33** as a pair of inseparable diastereomers (6 : 1) in 50% yield *via* a multiple-step approach from the chiral aldehyde **32**. For late-stage synthesis, the van Leusen reaction¹⁰¹ failed to transform the ketone into a nitrile, generating an intermediate in only 24% yield. Therefore, the Corey–Chaykovsky reaction was performed with compound **33** by utilizing Me_3SI and *t*BuOK in the presence of a solvent at room



Scheme 4 Synthesis 16,17,20-*epi*-deserpidine **36**.

temperature, which resulted in epoxide **34** (72%, confirmed by X-ray). Subsequently, the epoxide **34** underwent reductive ring opening to afford separable diastereomers **35a** (65%) and **35b** (23%). Isomers **35a** and **35b** were subjected to a multiple-step approach to accomplish 16,17,20-*epi*-deserpidine **36** (69%) and a lactone derivative **37** (50%) of (–)-deserpidine, respectively (Scheme 4).

2.2. Synthesis of terpene-based natural products

2.2.1. Synthesis of sesquiterpenoid-based natural products.

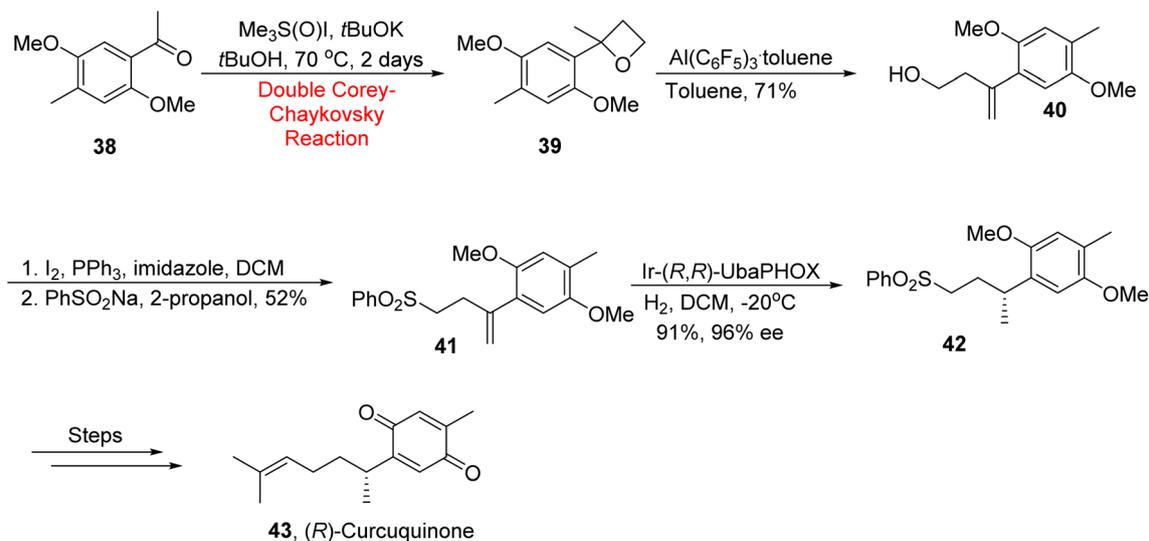
(*R*)-Curcuquinone **43** is a member of the bisabolene family of sesquiterpenes exhibiting anti-fungal and anti-microbial properties. In 2024, Bellido *et al.*¹⁰² documented the enantioselective formal synthetic route to (*R*)-curcuquinone **43** to illustrate the applicability of an improved methodology for the regioselective ring opening of oxetane utilizing Lewis superacid $\text{Al}(\text{C}_6\text{F}_5)_3$. Their strategy featured the Ir-catalyzed asymmetric hydrogenation approach *via* the Ir-UbaPHOX ligand¹⁰³ to induce chirality and a double Corey–Chaykovsky reaction to synthesize the key intermediates,¹⁰⁴ which were pivotal for the synthesis of targeted natural products.

The seven-step total synthesis of chiral curcuquinone **43** began with the conversion of the acetophenone **38** to *p*-

methoxyphenyl oxetane **39** *via* a double Corey–Chaykovsky reaction employing trimethylsulfoxonium iodide and *t*-butoxide in the presence of *t*-BuOH at 70 °C for 2 days to afford the oxetane **39**. Proceeding, the highly selective homoallylic alcohol **40** was achieved in 71% yield by the $\text{Al}(\text{C}_6\text{F}_5)_3$ -catalyzed regioselective ring opening of oxetane **39** in toluene. Subsequently, homoallylic alcohol **40** was treated with iodine, triphenylphosphine and imidazole through the Appel reaction, followed by sodium phenyl sulfinate substitution to generate homoallylic sulfone **41** in 52% yield. The Ir-catalyzed asymmetric hydrogenation of sulfone **41** gave the enantioselective compound **42** (91%, 96% ee). Then, the enantioselective product **42** was processed through a few steps to give (*R*)-curcuquinone **43** in 10% overall yield (Scheme 5).

Curcumene **49** belongs to the bisabolane family of sesquiterpenes,^{105,106} which displays a broad spectrum of bioactivities. They are widely recognized as traditional medicines^{107,108} and exhibit distinct enantiomeric properties. In particular, (*S*)- α -curcumene is used as an insecticide, whereas (*R*)- α -curcumene exhibits anti-tumor and anti-microbial properties.^{109,110} The stereogenic α -methyl aromatic moiety is the key feature of many natural products and pharmaceutical drugs. In 2023, Bellido *et al.*¹¹⁰ described the method for the asymmetrical total



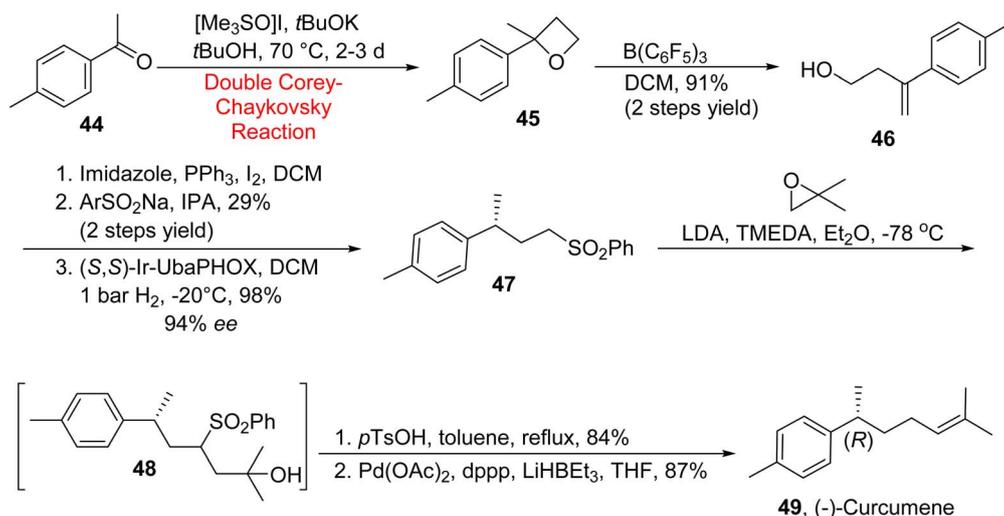


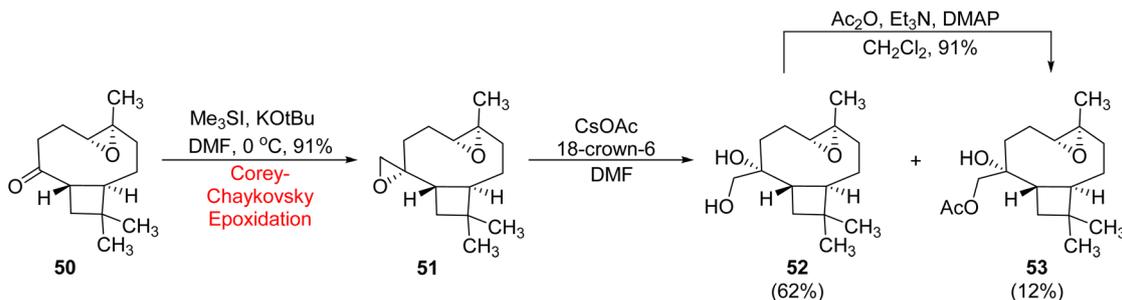
Scheme 5 Synthesis of (R)-curcuquinone (R)-43.

synthesis of (–)-curcumene **49**, involving the synthesis of homoallylic sulfones, Ir-catalyzed asymmetric hydrogenation and Corey–Chaykovsky reaction as pivotal steps. The homoallylic alcohols served as precursors for the synthesis of the corresponding homoallylic sulfones. In the foremost step, oxetane **45** was synthesized from aryl methyl ketone **44** via a double Corey–Chaykovsky reaction.¹¹¹ The $\text{B}(\text{C}_6\text{F}_5)_3$ -catalyzed regioselective isomerization of oxetane **45** generated homoallylic alcohol **46** in excellent yield (91% yield),¹¹² and the Appel reaction and nucleophilic substitution reaction yielded homoallylic sulfones. Subsequently, the iridium-catalyzed asymmetric hydrogenation of homoallylic sulfones was studied by utilizing a substrate and Ir-Ubaphox catalyst $\{[(4S,5S)\text{-Cy2-Ubaphox}]\text{Ir}(\text{COD})\}$ BAR_F (C1),¹¹³ to obtain γ -chiral sulfones. The reaction proceeded effectively at 1 bar H_2 , with 93% ee yield obtained at room temperature.¹¹⁴ By increasing pressure (15–50 bar), the enantioselectivity of the reaction reduced due to

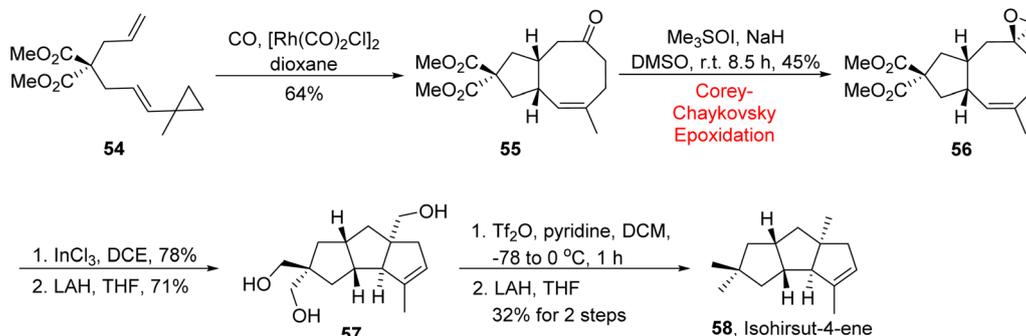
isomerization,¹¹⁵ whereas it increased by lowering the temperature to -20 °C up to 97% ee. The α -deprotonation of γ -chiral sulfones utilizing LDA/TMEDA, followed by alkylation with 2,2-dimethyloxirane,¹¹⁶ afforded **48** as a 2 : 1 mixture of diastereomers. The dehydration of **48** yielded an olefin under reflux conditions. In addition, the sulfone group was eliminated using a Pd-catalyzed methodology involving LiHBET_3 (superhydride) under mild conditions,¹¹⁷ thereby resulting in (R)-(–)-curcumene **49** in 72% yield (Scheme 6).

Linariophyllenes A–C were isolated from *Evolvulus linarioides*, which belong to the caryophyllane-type sesquiterpenoid family. The biosynthetic modifications of β -caryophyllene or its oxide result in the generation of these natural products. Linariophyllenes A–C have been found to exhibit anti-inflammatory properties, particularly linariophyllene B.¹¹⁸ In 2023, Stakanovs *et al.*¹¹⁹ developed a semisynthetic approach to synthesize linariophyllenes A–C by harnessing easily accessible

Scheme 6 Synthesis of (R)-(–)-curcumene **49**.



Scheme 7 Synthesis of linariophyllene C 53.



Scheme 8 Synthesis of isohirsut-4-ene 58.

and cost-effective sesquiterpenoid starting materials.^{120–125} The total synthesis of linariophyllene C employed Corey–Chaykovsky epoxidation as one of the significant steps. The synthesis commenced with the stereo-selective Corey–Chaykovsky epoxidation of kobusone 50 utilizing trimethylsulfonium iodide with KOtBu as the base in DMF, at 0 °C to achieve diepoxide 51 in 91% yield and increased stereoselectivity. Subsequently, the ring opening of one of the epoxides of diepoxide 51 in the presence of CsOAc and 18-crown-6 at a high temperature produced the diol 52 as the main product in 62% yield and acetate 53 in 12% yield. The desired acetate 53 was also synthesized from diol 52 in 91% yield using a standard acetylation procedure (Scheme 7).

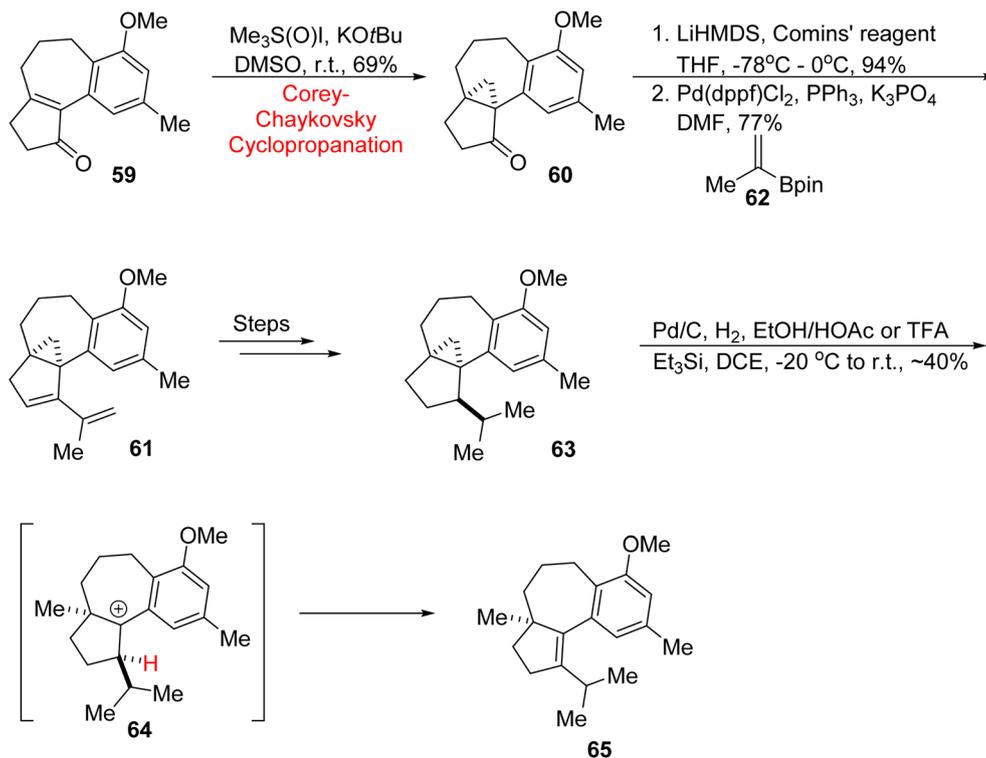
Isohirsut-4-ene 58 is a linear triquinane-based natural product characterized by tricyclic skeletons, which displays a wide range of biological properties. The synthesis of such triquinanes and their congeners could be noteworthy for pharmaceutical and biological research. Ikeda's group¹²⁶ isolated isohirsut-4-ene and isohirsut-1-ene from engineered bacteria. In 2022, Liu *et al.*¹²⁷ disclosed the first total synthesis of isohirsut-4-ene 58 with a 5/5/5 tricyclic core, confirming the proposed structure. Prior to this study, their structures had not been determined, and even Kutateladze¹²⁸ and Tantillo¹²⁹ had only predicted their relative configuration *via* computational NMR data. Liu and co-workers developed a new transannular strategy based on the [5 + 2 + 1] reaction^{130–132} for linear triquinanes (isohirsut-4-ene). The synthesis featured a [5 + 2 + 1] cycloaddition, the Corey–Chaykovsky reaction, and

a transannular epoxide–alkene cyclization to construct the key framework of a natural product.

The six-step total synthesis of 58 began with the preparation of starting compound 54, *i.e.*, ene-VCP (DEC tethered enevinylcyclopropane)^{133,134} in a single step. Then, the [5 + 2 + 1] reaction was carried out under optimized conditions to obtain a pure diastereomer of 5/8 bicyclic product 55 (64% yield). Compound 55 was then transformed into epoxide 56 (45% yield) *via* the Corey–Chaykovsky reaction under standard conditions (NaH, DMSO, trimethylsulfoxide iodide). A transannular epoxide–alkene cyclization of epoxide 56 utilizing the InCl₃ catalyst afforded a 5/5/5-fused tricyclic product, followed by the LiAlH₄-promoted reduction that resulted in a triol product 57 (71% yield). Compound 57 was converted into trifluoro-methanesulfonate ester, followed by the reduction of all three hydroxyl groups of esters *via* LAH, thereby furnishing the desired product, isohirsut-4-ene 58, in 32% overall yield. The NMR spectral results of synthetic compound 58 were determined to be consistent with the literature data. The strategy was further extended to synthesize other congeners of linear triquinanes (Scheme 8).¹³⁵

2.2.2. Synthesis of diterpenoid-based natural products. Hamigerans belong to the family of diterpenoids, displaying significant biological and structural activities. Cambie and his colleagues first isolated numerous hamigeran natural products from *Hamigera tarangaensis*.^{136–140} This family structurally exhibits tricyclic cores of two types, 6–6–5 and 6–7–5, featuring a polysubstituted and brominated aromatic ring. *In vitro*, hamigeran B exhibits potent inhibitory action against the





Scheme 9 Synthesis of compound 65.

replication of polio and herpes virus, and hamigeran G 7 shows inhibition against the growth of HL-60 (leukemia) cell line. Early research focused on the 6–6–5 tricyclic core of hamigeran A and B, which led to several efficient total syntheses. However, the challenge of synthesizing seven-membered rings resulted in fewer reports focusing on the synthesis of hamigerans with a 6–7–5 carbon core.

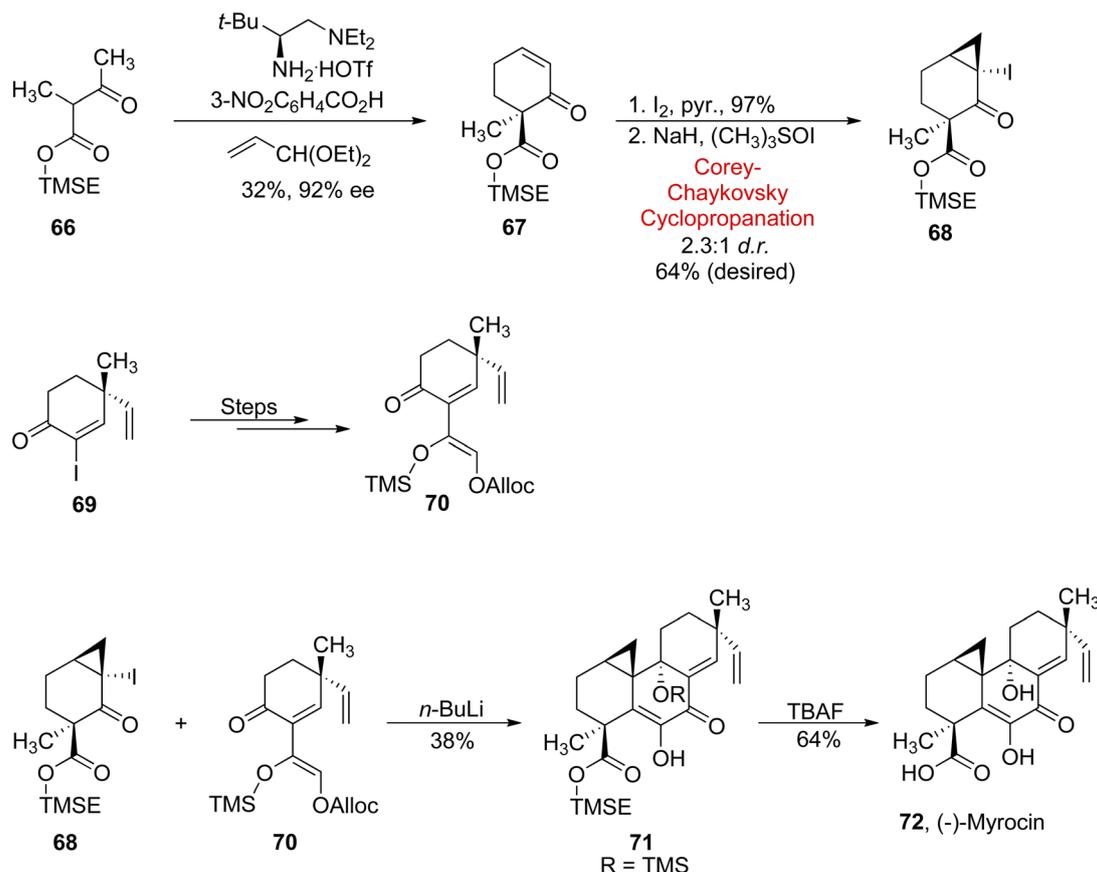
In 2016, Gao *et al.* revealed the first total synthesis of hamigeran G by employing (*R*)-piperitone, followed by the Suzuki and McMurry coupling to afford a key intermediate.¹⁴¹ Subsequently, in 2018, Stoltz and colleagues¹⁴² reported the total syntheses of hamigeran C and D through a Pd-catalyzed asymmetric decarboxylative allylation and other key steps. In 2020, Jiang *et al.*¹⁴³ devised a synthetic strategy for the construction of a 6–7–5 three-cyclic carbon framework of hamigeran natural products. Their first attempt featuring 5-bromovanillin 144 as the starting material did not work out, as they were unsuccessful in reducing the tetrasubstituted double bond. In the second attempt, Jiang and his group envisioned the selective C–C bond cleavage of cyclopropane as a masked CH_3 group. Their synthetic route commenced with the Corey–Chaykovsky cyclopropanation¹⁴⁵ of symmetric tricyclic enone 59, utilizing the trimethylsulfoxonium iodide reagent with $\text{KO}t\text{Bu}$ base in DMSO at room temperature to afford tetracyclic compound 60 in 69% yield. Subsequently, compound 60 was transformed into vinyl triflate in 94% yield in the presence of Comins' reagent and LiHMDS in THF at -78°C to 0°C , followed by Suzuki coupling with 62 in DMF that resulted in diene 61 in 77% yield. Thereafter, the diene 48 underwent a sequence

of steps to afford 63, which was subjected to hydrogenation conditions in a mixture of CH_3COOH and ethanol or THF and triethylsilane in DCE to afford benzylic cation 64 initially due to the acidic conditions. Later, benzylic cation 64 was transformed into the desired product 65 in 40% yield *via* deprotonation. Although the saturation of the tetrasubstituted double bond of intermediate 65 and the selective cleavage of the C–C bond in cyclopropane 63 could not be achieved, the reported synthetic pathway led to the construction of a tricyclic carbon core (6–7–6) of hamigeran natural products (Scheme 9).

In 1989, myrocins were first discovered in culture filtrates of the soil fungus *Myrothecium verrucaria*, which belongs to the family of anti-proliferative and antibiotic pimarane diterpenes.^{146,147} (+)-Myrocin C and (–)-myrocin B were the first isolated metabolites that showcased antibiotic effect towards Gram (+) bacteria, fungi and yeast.^{148,149} The structural analogs of metabolite 5–7 were isolated from cultures of marine and soil fungi, and they exhibited comparable antibiotic effects.^{150–153} In 1993, Danishefsky and Chu-Moyer unveiled the pivotal total synthesis of (±)-myrocin C.^{154,155} Later, Yamada and co-workers presented their research regarding myrocin C.¹⁵⁶ Prompted by the hypothesis of Chu-Moyer–Danishefsky that myrocin C could crosslink DNA¹⁵⁷ and following the Hoffmann *et al.*^{158,159} model, Tomanik and co-workers¹⁶⁰ reported the synthesis of (–)-myrocin G recently. In 2020, Tomanik *et al.*¹⁶¹ documented the synthetic pathway for myrocin G, involving the Corey–Chaykovsky reaction as one of the key steps.

The total synthetic pathway of (–)-myrocin G includes the complex stereoselective fragment coupling–cyclization cascade





Scheme 10 Synthesis of (-)-myrocin G 72.

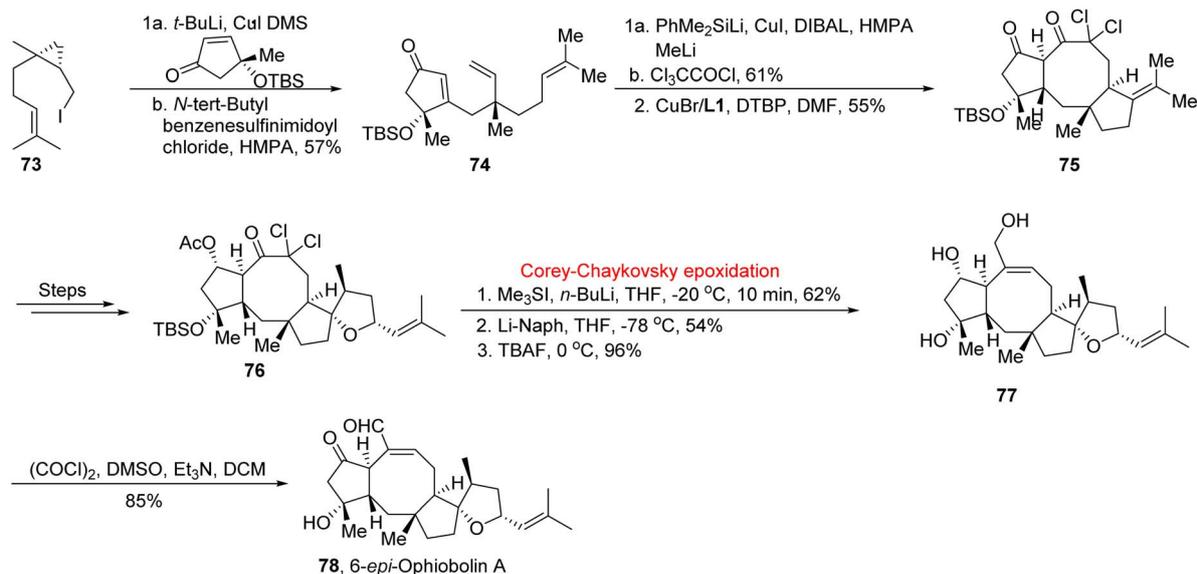
of iodocyclopropane **68** and α -iodoenone **71**. In the first step, the preparation of iodocyclopropane **68** began with the asymmetric Robinson annulation¹⁶² of the β -ketoester **66** with diethyl acrolein to afford an enone **67** (32%, 92% ee). Next, the enone **67** was subjected to dehydroiodination by the aid of I_2 and pyridine, followed by the Corey–Chaykovsky cyclopropanation employing trimethylsulfoxonium iodide and NaH base, which furnished the enantioenriched iodocyclopropane **68** (*d.r.* = 2.3 : 1) in 68% yield. Secondly, the unsaturated ketone **69** underwent a six-step process to prepare the C-ring coupling fragment **70** in 19% overall yield. Subsequently, the cyclodehydration (tandem coupling) of **68** and **70** resulted in the desired diosphenol **71** in 38% yield. Lastly, the global deprotection of **71** employing TBAF delivered the (-)-myrocin G **72** in 64% yield (Scheme 10).

2.2.3. Synthesis of sesterterpenoid-based natural products. The ophiobolins are bioactive 5,8,5-fused sesterterpene-based natural products that are extracted from fungal pathogens (*Aspergillus* and *Bipolaris* genus).^{163–165} In particular, ophiobolin A **78** is highly cytotoxic against breast cancer (MCF-7), multidrug-resistant leukemia (MDR HL-60), glioblastoma multiforme (GBM) and thirty other cell lines. The 6-*epi*-ophiobolin A **78** epimer also exhibits cytotoxic activity, and a cell-line-specific relationship has been found between C6 stereochemistry and anti-cancer activity.

Regardless of the significance of ophiobolin in the synthetic community, only three ophiobolin syntheses were reported in

the last 30 years before 2020.^{166,167} Thach *et al.*¹⁶⁸ in 2020 introduced a 14-step pathway to (+)-**78**, utilizing a radical cascade approach. Their successful synthetic strategy expanded the synthesis of a number of key structural derivatives of ophiobolins. Thach's total synthesis commenced with the preparation of a geraniol-derived cyclopropyl iodide **73** (*via* Charette's protocol),^{169,170} which was transformed into a ring-opened lithiate and was coupled with the (-)-linalool-derived enone **74**, resulting in an enolate intermediate. In the following step, the enolate was quenched with *N*-tert-butylbenzenesulfinimidoyl chloride (Mukaiyama's reagent), forming the corresponding enone **74** directly.¹⁷¹ The highly selective 1,4-reduction enabled by $\text{PhMe}_2\text{SiCu-H}$ and *C*-acylation with Cl_3CCOCl , followed by radical cyclization *via* di-*tert*-butylbipyridine-ligated Cu, afforded the polycycle **75** in 55% yield on isolation. Compound **75** then underwent a sequence of reactions to ultimately yield the *trans*-addition product **76**. Compound **76** was further treated *via* four steps involving a final approach to accomplish the total synthesis of 6-*epi*-ophiobolin A **78**. The treatment of carbonyl C7 of **76** with Me_3Si and *n*-BuLi at -20°C for 10 min generated the Corey–Chaykovsky epoxide in the presence of THF, followed by tandem reductive epoxide opening, dehalogenation and silyl ether deprotection (TBAF), which produced the triol intermediate **77** (52% yield). Lastly, the Swern oxidation of intermediate **77** afforded the 6-*epi*-ophiobolin A **78** in 85% yield (Scheme 11).



Scheme 11 Synthesis of 6-*epi*-ophiobolin A 78.

2.2.4. Synthesis of apocarotenoid-based natural products.

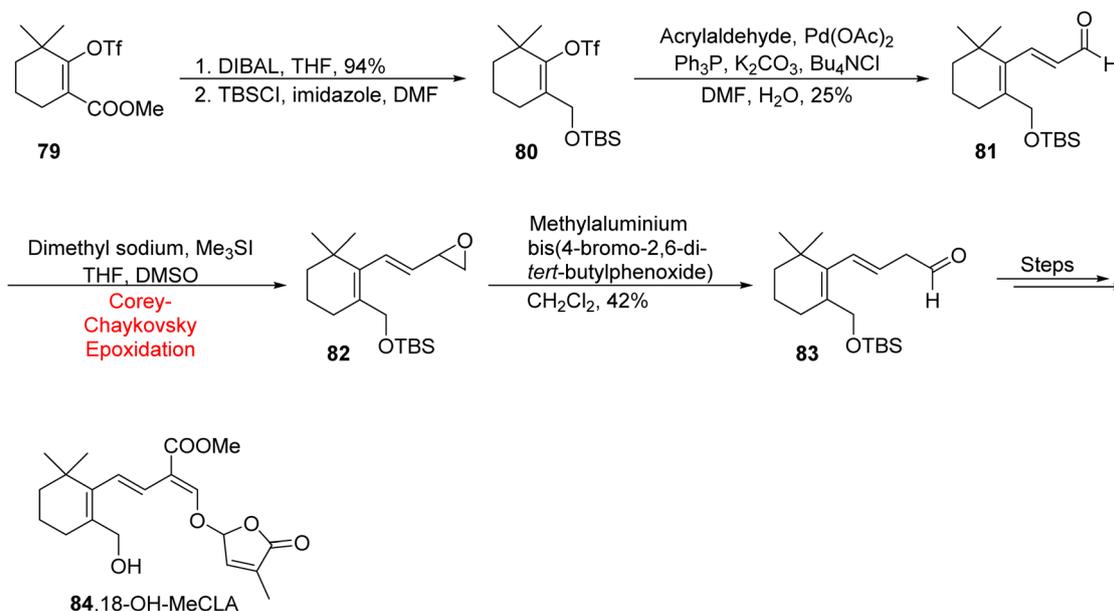
Strigolactones (SLs) (apocarotenoid compounds) are recognized as germination enhancers of root parasitic plants.¹⁷² They also show application potential as rhizosphere-signaling compounds for the AM (arbuscular mycorrhizal) symbiotic relationship.^{173,174} To date, about thirty strigolactones have been characterized from several plant root secretions.¹⁷⁵

In 2020, Mori *et al.*¹⁷⁶ successfully synthesized 18-OH-MeCLA 84 in eight steps, including the Corey–Chaykovsky as a pivotal step in the synthetic route. The synthesis began with the triflate ester 79, which was reduced with diisobutylaluminium hydride to give triflate alcohol, followed by the protection of the –OH group by a TBS [*tert*-butyl(dimethyl)silyl] group to obtain the

resulting silyl-protected triflate 80. The Heck reaction of silyl-protected triflate with acrolein afforded TBSO-C12-aldehyde 81. The silylated aldehyde 81 was treated further to attain TBSO-C13-aldehyde 82 *via* the Corey–Chaykovsky epoxidation upon reaction with dimethylsulfonium methylide and THF in DMSO, followed by MABR (methylaluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide))-promoted epoxide rearrangement to afford aldehyde 83. The aldehyde in the multiple-step process afforded 18-OH-MeCLA 84 (Scheme 12).

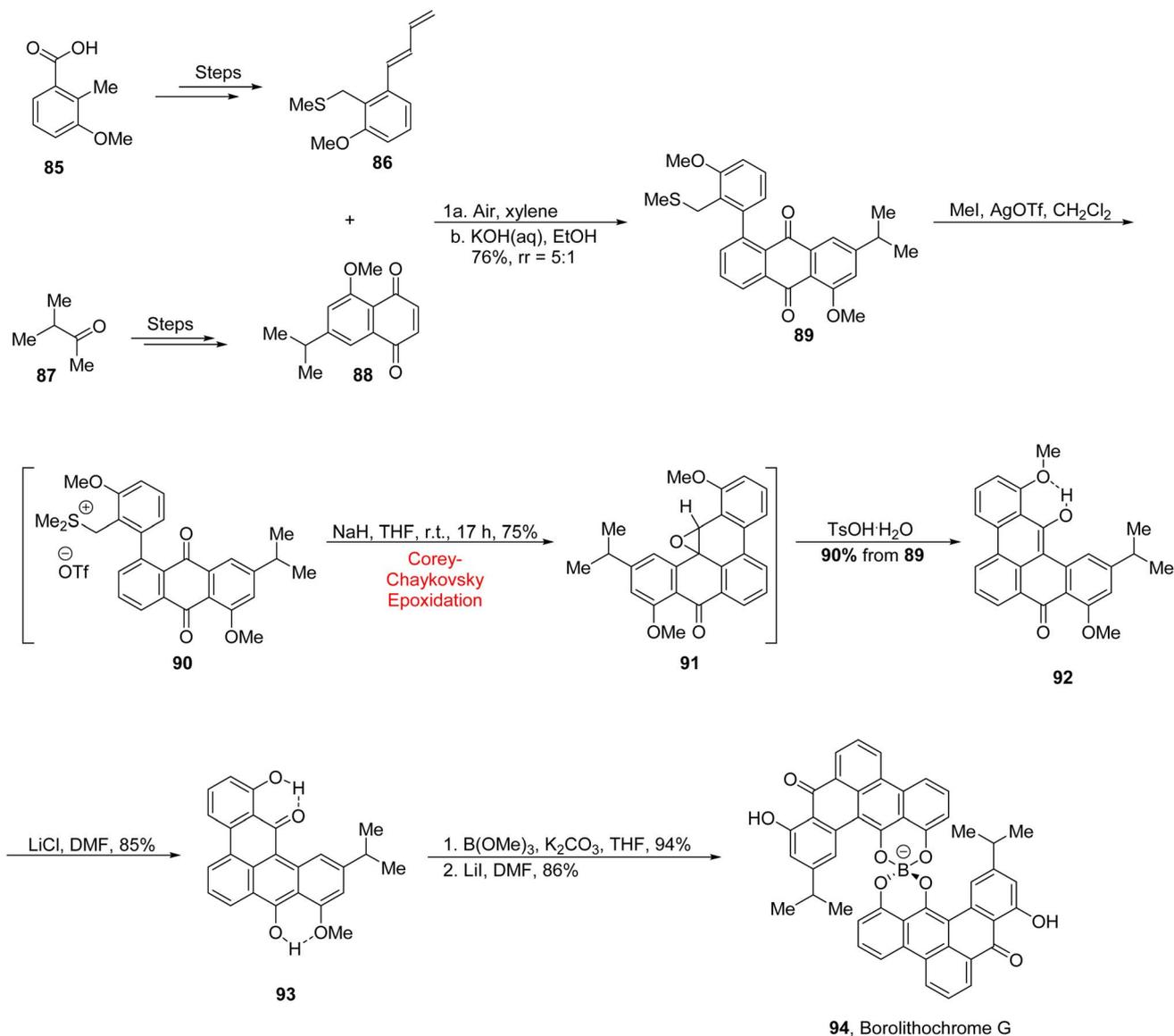
2.3. Synthesis of polyketide-based natural products

Borolithochromes are rare natural products composed of unique spiroborate cores, featuring two benzo[*gh*]tetraphene



Scheme 12 Synthesis of 18-OH-MeCLA 84.





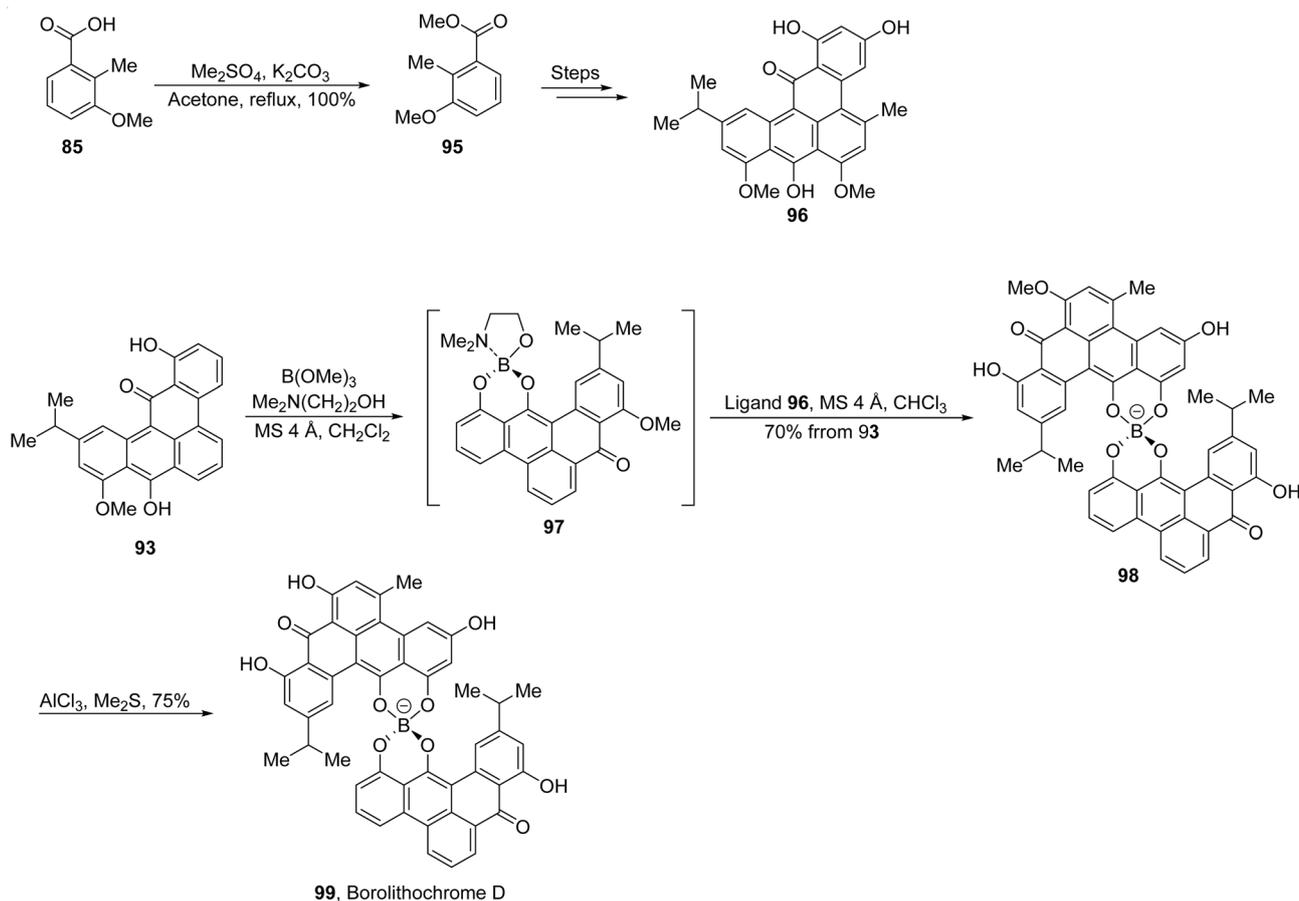
Scheme 13 Synthesis of borolithochrome G 94.

ligands.¹⁷⁷ These red pigments have been isolated from the remains of *Solenopora jurassica*¹⁷⁸ (Jurassic putative red alga). From this family, a racemic mixture of borolithochromes A, D, and G was isolated, whereas borolithochrome F was attained as a single enantiomer. Furthermore, the benzo[*gh*]tetraphene scaffold is rarely found in natural products, barring clostrubins A and B, which exhibit potent anti-bacterial properties.^{179,180} Likewise, it was expected that the ligands in borolithochromes also exhibit bioactivities. Due to the limited availability of isolated borolithochromes, the information regarding their bioactivities and notable structures was scarce, motivating scientists to develop the total synthesis methods for these pigments.

In 2024, Kirita *et al.*¹⁸¹ carried out the first total syntheses of borolithochromes A, D and G involving the Diels–Alder reaction for tricyclic intermediates, intramolecular Corey–Chaykovsky

reaction to construct pentacyclic ligand and spiroborate formation as one of the significant steps. Firstly, the synthetic route for borolithochrome G 94 involved the Diels–Alder reaction. The desired diene 86 and dienophile naphthoquinone 88 were prepared individually *via* a multiple-step approach using benzoic acid derivative 85 and isopropyl methyl ketone 87 as starting materials, respectively. Then, treating diene 86 and naphthoquinone 88 *via* the Diels–Alder reaction resulted in the formation of an anthraquinone 89 mixture (5 : 1) in 76% yield. In the next step, the mixture produced the sulfonium ion 90 on treating it with iodomethane. The sodium hydride was added at r.t. to the solution of sulfonium ion 90 in dry THF to facilitate the intramolecular Corey–Chaykovsky epoxidation, which afforded the pentacyclic epoxide 91 in 75% yield. The crude mixture 91 was rearranged under acidic conditions to give phenol 92 in 90% yield. Ultimately, the phenol 92 (ref. 182) was





Scheme 14 Synthesis of borolithochrome D 99.

subjected to multiple steps, resulting in the targeted natural product, borolithochrome G **94**, in 86% yield (Scheme 13).¹⁸³

The spiroborate of borolithochrome D (**99**) also consists of ligands of borolithochrome A and D. Thus, the synthesis of a heterocomplex was achieved by the stepwise substitution of ligands in borate, which involved the boron:aromatic (1:1) ligand complex intermediate. The synthesis involved the coupling of ligands **93** (obtained *via* Corey–Chaykovsky reaction) and **96**. Initially, the monomer complex **97** was prepared by treating ligand **93** with trimethyl borate in the presence of *N,N*-dimethylethanolamine. Then, the ligand **96** was complexed with **97** to form a mixed complex, which was further subjected to *O*-demethylation using AlCl_3 to afford the borolithochrome D **99** in 75% yield (Scheme 14).

In 2024, Kirita *et al.*¹⁸⁴ first reported the method for the total syntheses of optically pure borolithochromes I1 (**105**) and I2 (**106**) involving the Diels–Alder reaction, Corey–Chaykovsky reaction and boron complexation as key steps. The synthetic route began with the synthesis of a common pentacyclic ligand. Firstly, the naphthoquinone **101** was prepared from (*S*)-2-methylbutanol **100** *via* TEMPO oxidation¹⁸⁵ in six steps. Subsequently, the naphthoquinone **101** and diene **86** were subjected to the Diels–Alder reaction under basic conditions to give the product in 62% yield, followed by *S*-methylation to give

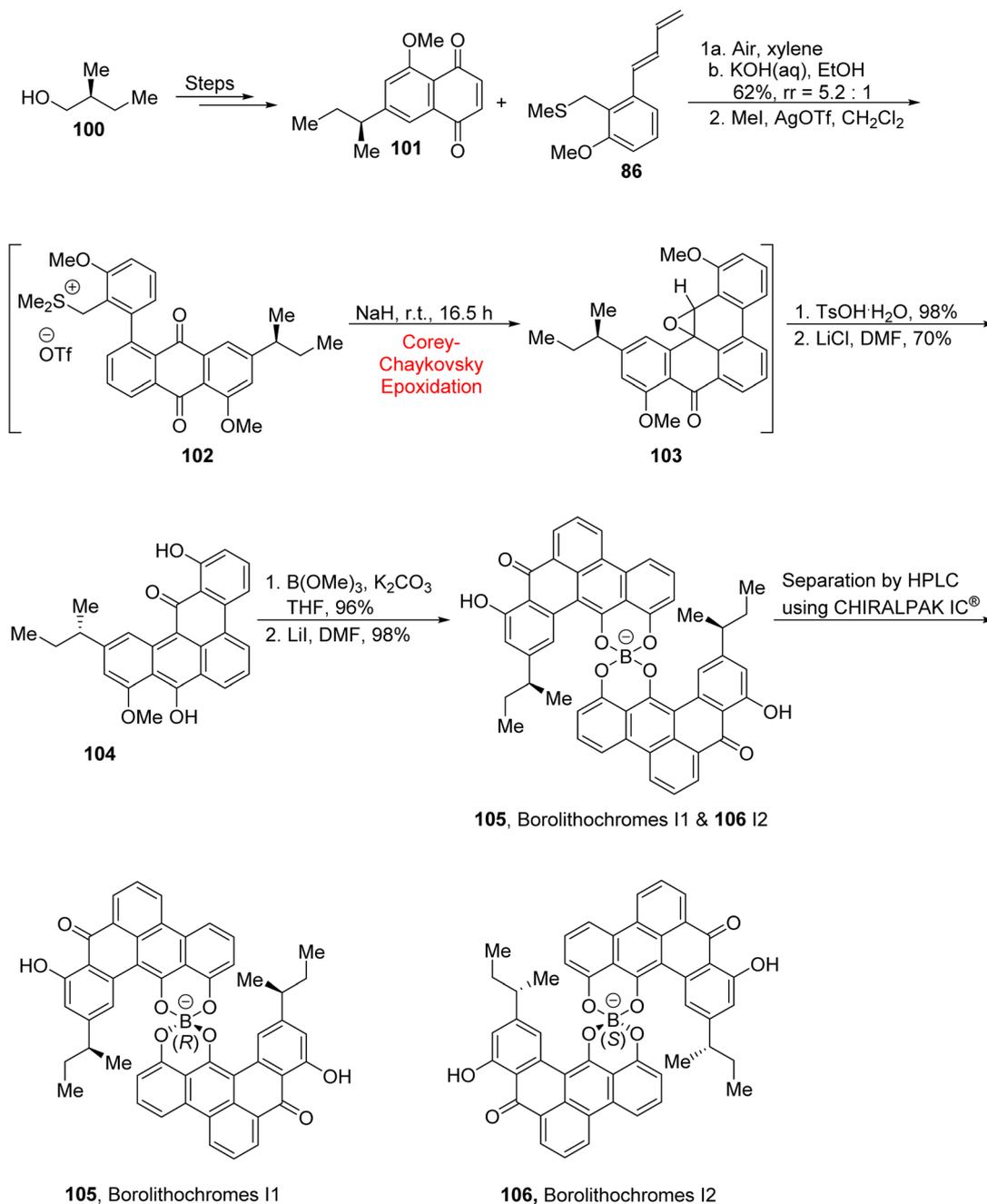
sulfonium ion **102**. NaH was added to the sulfonium ion **102** in dry THF at r.t. to facilitate the intramolecular Corey–Chaykovsky epoxidation,¹⁸⁶ which gave the pentacyclic epoxide **103** in 75% yield. The epoxide **103** then underwent rearrangement¹⁸⁷ and gave the product in 98% yield, followed by C-selective *O*-demethylation with LiCl in DMF, which resulted in the pentacyclic ligand **104** in 70% yield.^{188,189}

Moving forward, the monomethyl ether **104** was treated with B(OMe)_3 in potassium carbonate to give the product in 96% yield, followed by *O*-demethylation *via* LiI in DMF to produce the mixture of borolithochromes I1 (**105**) and I2 (**106**) in 98% yield.¹⁸² Ultimately, the diastereomeric mixture was separated by HPLC *via* CHIRALPAK IC to give optically pure borolithochrome I1 **105** and I2 **106** (Scheme 15).

2.4. Synthesis of cyclic depsipeptide-based natural products

Arenastatin A is a cytotoxic cyclic depsipeptide, first isolated from *Dysidea arenaria* Okinawan marine sponge in 1994.¹⁸² Total synthesis and NMR analyses have been employed to determine its structure.^{190,191} Depsipeptides are members of the cryptophycin family that display potent cytotoxic behavior.¹⁹² Cryptophycin-52, a powerful analog, was discovered by extensive medicinal research. The cytotoxicity of arenastatin A and its related analogs is influenced by the stereochemistry of the





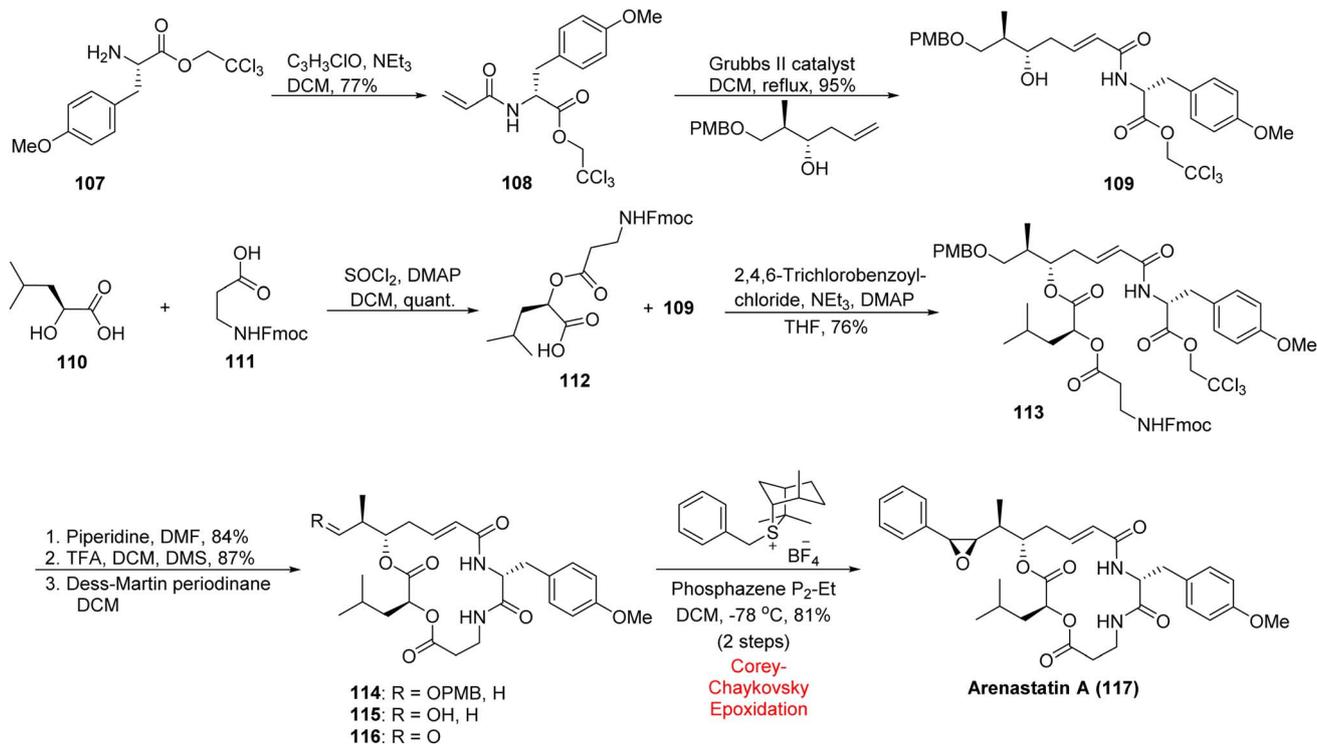
Scheme 15 Synthesis of borolithochrome I1 105 and I2 106.

compounds. The 7,8-epoxide moiety is crucial in the compounds, as its (7*S*,8*S*) epimer is inactive. Previously, this moiety was achieved either *via* *m*-CPBA/dioxirane oxidation or cyclization of bromohydrin, which resulted in isomeric mixture that required separation and relatively long synthetic routes, respectively. However, Aggarwal *et al.*¹⁹³ devised an efficacious technique to construct a stereoselective epoxide (>99:1 d.r.) moiety *via* CCR using the chiral sulfonium salt.

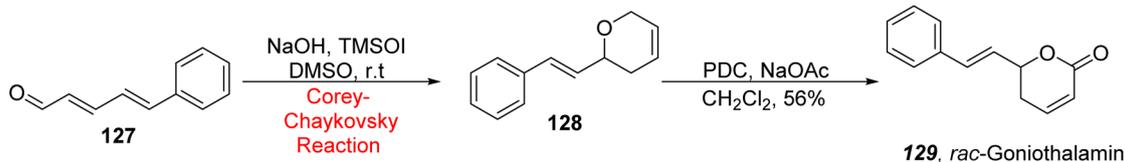
In 2024, Mihara *et al.*¹⁹⁴ proposed an optimized synthetic route for the total synthesis of arenastatin A 117 and analogs of segments B, including the construction of the 7,8-epoxide

moiety using the Corey–Chaykovsky reaction. The synthetic route began with the assembly of the four segments A–D. Firstly, (*R*)-*O*-methyltyrosine 107 was transformed into an acrylamide (77%) using $\text{C}_3\text{H}_3\text{ClO}$ and NEt_3 in DCM. The acrylamide went through cross-metathesis with segment A, employing Grubbs II catalyst on reflux, producing segment AC 109 (95%). On the other hand, Fmoc- β -alanine 111 (segment D) was coupled with *L*-leucic acid 110 using SOCl_2 and acyl chloride (segment B) to give the segment BD 112. Then, the assembly of two segments following the Yamaguchi esterification technique resulted in the cyclization of precursor 113, which, on Fmoc removal with





Scheme 16 Synthesis of arenastatin A 117.

Scheme 17 Synthesis of *rac*-goniothalamin 129.

piperidine¹⁹⁵ and macrocyclization, led to macrolactam **114** (84%). Lastly, the PMB was subjected to cleavage *via* TFA, followed by the Dess–Martin oxidation to afford the aldehyde **116**. The treatment of aldehyde **116** with a chiral sulfonium salt *via* the Corey–Chaykovsky epoxidation using phosphazene P₂–Et in DCM at –78 °C produced arenastatin A **117** in 81% yield, with complete stereoselectivity (Scheme 16).

2.5. Synthesis of styryl-lactone-based natural products

5,6-Dihydro-2*H*-pyran-2-one, 3,6-dihydro-2*H*-pyran (DHP) and tetrahydropyran (THP) are six-membered oxygen heterocycles, which are ubiquitous core units of a variety of natural products. *R*-(+)-Goniothalamin **129**, a 5,6-dihydro-2*H*-pyran-2-one derivative, exhibits cytotoxic properties. In 2022, Kumar *et al.*¹⁹⁶ reported a transition-metal-free approach to generate 3,6-dihydro-2*H*-pyran derivatives *via* a modified Corey–Chaykovsky reaction. It involved the synthesis of the desired epoxy cyclopropane from corresponding enones.

The two-step synthesis of racemic goniothalamin **129**, an anti-tumor agent, commenced with a styryl-substituted α,β -

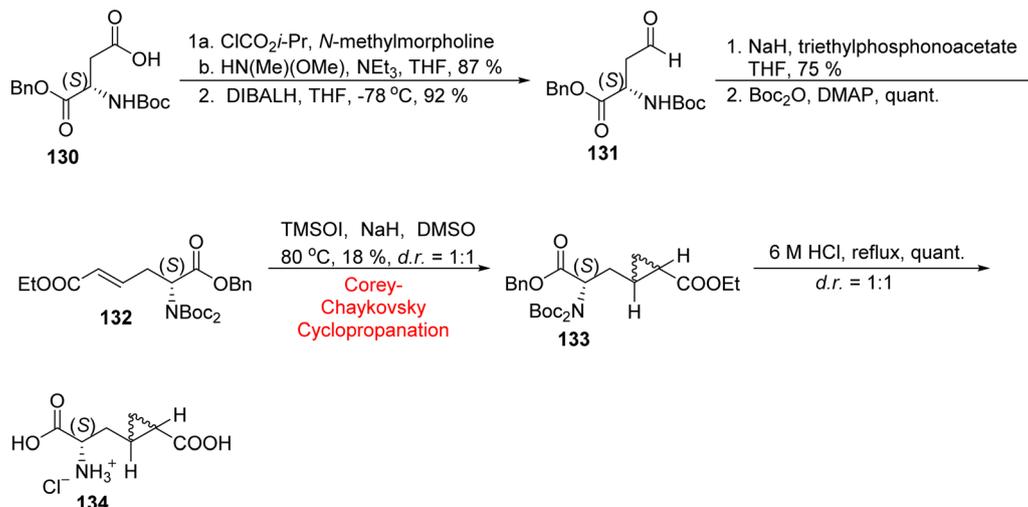
unsaturated aldehyde **127**, which was subjected to an extended Corey–Chaykovsky reaction using the sulfoxonium ylide and sodium hydroxide in DMSO to afford **128** at room temperature. Following this, compound **128** underwent oxidation to yield **129** (5,6-dihydro-2*H*-pyran-2-one) in the presence of PDC and sodium acetate in DCM (Scheme 17).

2.6. Synthesis of amino acid-based natural products

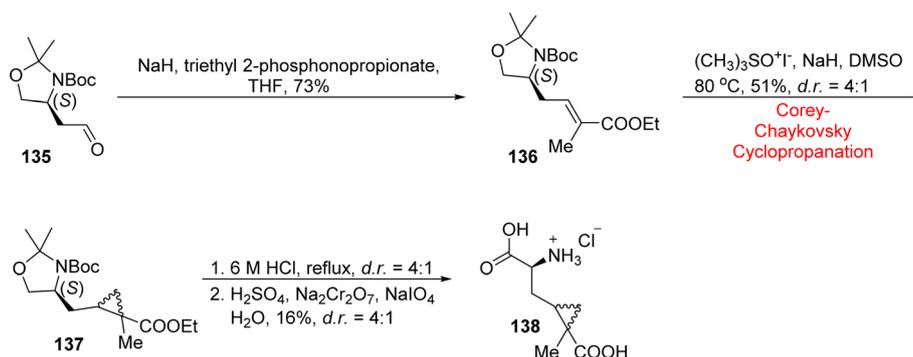
(2*S*)-Aminoadipic acid (AA), a homologue of (*S*)-glutamate, is a broad-spectrum endogenous agonist of mGluR. Madsen and co-workers¹⁹⁷ reported (*S*)-AA as a potent selective agonist for mGlu2. In 2024, Staudt *et al.*¹⁹⁸ documented their strategy to synthesize conformationally restricted hybrid structures of (*S*)-AA analogs. The synthetic route of these analogs featured a Corey–Chaykovsky reaction as one of the crucial steps.

The synthesis of (*S*)-AA analog **134** was initiated by the strategic protection of (*S*)-aspartate **130** to achieve Weinreb-amide, which was subjected to selective reduction to yield the desired aldehyde **131** in 92% yield. The Horner–Wadsworth–Emmons reaction of aldehyde **131** resulted in the *E*-isomer of unsaturated





Scheme 18 Synthesis of (S)-AA analog 134.



Scheme 19 Synthesis of the 5-methyl analog 138.

ester, followed by the double Boc-protection of the amine with DMAP to yield **132**. The *in situ* Corey–Chaykovsky reaction of **132** was carried out employing $(\text{CH}_3)_3\text{SOI}^-$ and sodium hydride to afford a 1:1 mixture of **133** in DMSO at 80 °C in 18% yield. Ultimately, the global deprotection of **133** in 6 M HCl on reflux resulted in the desired (S)-AA analog **134** with a 1:1 mixture of diastereomers (Scheme 18).

The synthesis of the 5-methyl analog **138** began with the olefination of commercially available aldehyde **135**, utilizing triethyl 2-phosphonopropionate and NaH, in the presence of THF to furnish the single stereoisomer of compound **136** in 73% yield. Subsequently, the Corey–Chaykovsky reaction of **136** was carried out to accomplish a 4:1 diastereomeric mixture of the 5-methyl-cyclopropane analog **137** in 51% yield employing TMSOI, sodium hydride and DMSO at 80 °C. Lastly, the global deprotection of analog **137** in 6 M HCl under reflux, followed by Jones-oxidation, afforded the desired analog **138** in 16% yield (4:1 d.r.) (Scheme 19).

2.7. Synthesis of hybrid natural products

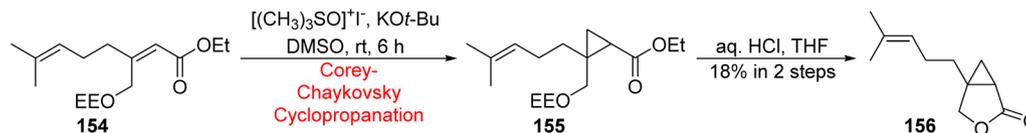
2.7.1. Monoterpene indole alkaloids.

In 2019, Zhang and colleagues¹⁹⁹ first isolated (–)-hunterine A **144** from *Hunteria*

zeylanica, which belongs to the terpenoid indole alkaloid class with a characteristic 6/7/6/6/5 pentacyclic framework featuring an exotic 7-membered 2,3,4,5 tetrahydro-1*H*-azepine bridge scaffold.^{200–202} The sparse amount of available alkaloid optically described the bioefficacy of (–)-hunterine A, which exhibited cytotoxicity against HepG2.¹⁹⁹ Zhang *et al.* reported a feasible biogenetic route for the synthesis of **144** using tuboxenine as the starting material.

In 2024, Zsigulics *et al.*²⁰³ pursued the bioinspired total synthesis of (–)-hunterine A (**144**) by addressing the selectivity challenges *via* the aspidosperma core unit. The total synthesis was achieved through an interim template technique carried out without a direct group, featuring the ring-opening cascade and the Corey–Chaykovsky reaction as critical steps to construct the epoxide intermediate. The bioinspired synthesis began with the modified Stork's tricyclic ketone **139**, which was subjected to selective hydrolysis and decarboxylation under acidic conditions, followed by Fischer indolization that produced indolenine **140** in 48% yield (2 steps). Then, the Boc-protection of indolenine **140** after deprotonation with LDA at –78 °C gave the product in 87% yield. Next, the partial reduction of the ester moiety in 2 steps (reduction *via* DIBAL-H in toluene at –78 °C





Scheme 22 Synthesis of the analog of damascenolide™ 156.

with variable glycosylation or oxidation states have also been isolated. Hypocretenolides feature an α -methylene- γ -lactone core exhibiting a distinct bridged 5/7/6 ring system. Prior research confirmed that these natural products are active against cancer metastasis^{207,208} as they depicted low IC₅₀ values against multiple tumor cell lines and suppressed the activation of NF- κ B.^{209,210} Regardless of the potential efficacy of hypocretenolides, further evaluation had been hindered due to their limited quantity; moreover, no total synthesis of hypocretenolides had been reported, impeding structure–activity relationship (SAR) studies and the development of potential derivatives.

To circumvent this limitation, Chen *et al.*²¹¹ in 2024 devised an efficient approach for the first collective total synthesis of four hypocretenolides, involving the Corey–Chaykovsky reaction as a key step to introduce the cyclopropane moiety. The synthesis was initiated with the economical feedstock (*S*)-carvone **146**, which underwent the Corey–Chaykovsky reaction with Me₃SOI and sodium hydride in DMSO at 50 °C to afford cyclopropane ring **147** in 96% yield. The cyclopropane-endowed compound **147** was treated over a number of steps to afford the allylic chlorinated product **148**. The alkene lithium obtained from compound **149** mounted a nucleophilic attack on compound **148**, followed by TBAI-induced alkylation and desilylation to afford an alcohol **150** in 30% yield. Then, DMP oxidation of **150** gave aldehyde in 80% yield, followed by oxime intermediate formation with NH₂OH·HCl. The intermediate was subjected to intramolecular 1,3-dipolar cycloaddition, which gave the isoxazoline product **151** in 75% yield with the desired 5/6/7 ring system. In the next step, the isoxazoline ring was subjected to Fe/AcOH reduction, which gave the desired dienone **152** in 87% yield. The dienone **152** was treated over several steps to furnish hypocretenolide **153** (Scheme 21).

Damascenolide™ [4-(4-methylpent-3-en-1-yl)furan-2(5*H*)-one] is isolated from *Rosa damascena* (damask rose),²¹² with a characteristic citrus-like odor that imparts blooming and natural aroma character to artificial rose. Miyazawa *et al.* explored the SOR (structure–odor relationships) of a total of 24 analogs of damascenolide™ and studied their syntheses for developing more aroma compounds.^{213,214} Their previous research on the analogs of damascenolide™ revealed that slight structural changes significantly influenced the odor.

In 2021, Miyazawa *et al.*²¹⁵ synthesized 10 analogs of damascenolide™ and performed odor evaluation; the analogs were divided into 3 groups (dimethylated, cyclopropanated and other analogs). Group 2, featuring cyclopropanated analogs, was selected because previous evaluation showed that cyclopropanation alters the odor of various odor-active compounds. Initially, Miyazawa *et al.* attempted to synthesize

cyclopropanate damascenolide™ but failed. However, the Corey–Chaykovsky cyclopropanation was successfully used to synthesize cyclopropane **156**. The synthetic intermediate of damascenolide™ **154** was subjected to the Corey–Chaykovsky reaction using trimethylsulfoxonium iodide and KOt-Bu in DMSO at room temperature to yield compound **155**. The EE group of compound **155** was removed using aqueous HCl in THF, followed by one-pot lactonization to afford compound **156** in 18% yield (2 steps) (Scheme 22).

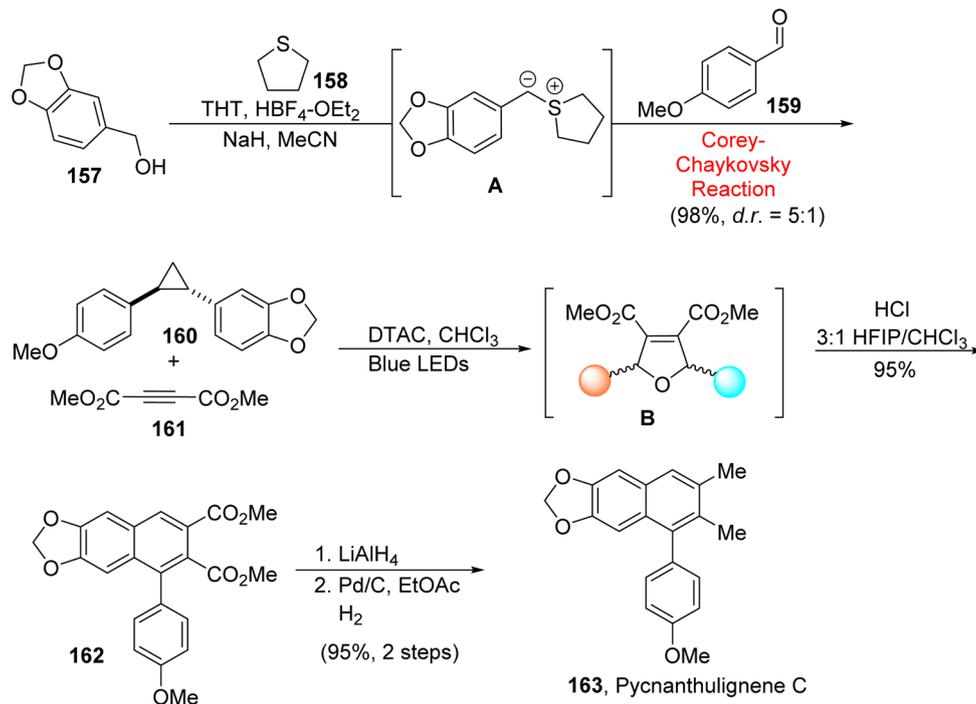
3 Miscellaneous

Classical lignans, specifically caryltetralin, aryl-naphthalene and dihydronaphthalene, are bioactive natural products.²¹⁶ The utilization of their synthetic derivatives as pharmaceutical agents prompted research efforts into their synthetic strategies. The variety of existing methods for preparing natural complexes often fall short in interrogating the SAR (structure–activity relationship). Therefore, modern techniques emphasize diversity and modularity. Alfonzo and co-workers reported a unified method that utilized THFs (tetrahydrofurans) as key scaffolds to synthesize various CLs and their subtypes.²¹⁷

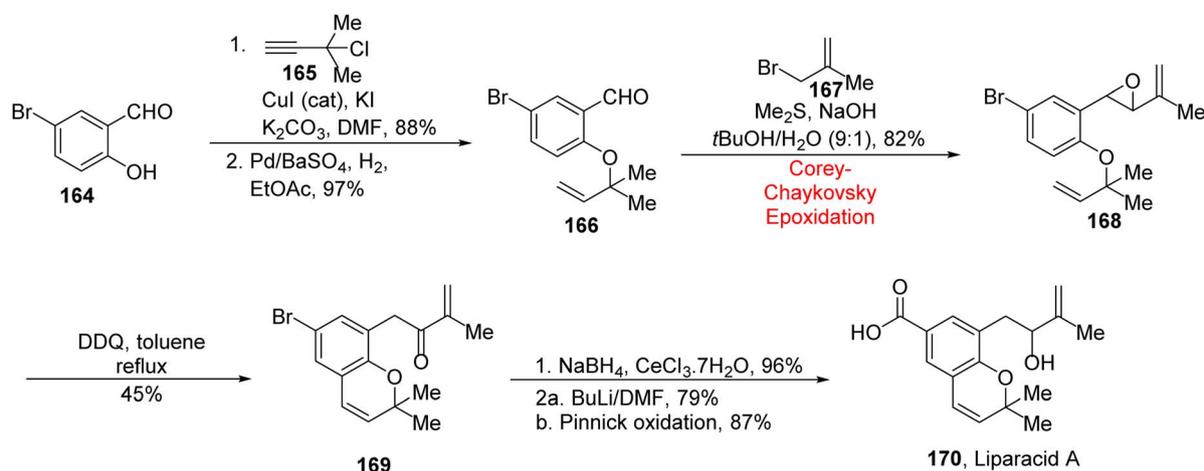
In 2020, Alfonzo *et al.*²¹⁸ reported that a modular one-pot method enabling the efficacious synthesis of aryl-naphthalene and dihydronaphthalene natural products can be carried out with simply accessible precursors (epoxides and dipolarophiles) covering multiple oxidation states, *e.g.*, pycnanthulignene C. These are also known to exhibit anti-microbial action against a range of drug-resistant microbes.²¹⁹ The total synthesis of pycnanthulignene C **162** involved the Corey–Chaykovsky reaction and photoredox-catalyzed [3 + 2] cycloaddition as key steps. Firstly, sulfonium ylide **A** was prepared by treating the benzyl alcohol **157** with tetrahydrothiophene **158** and HBF₄·OEt₂, then with NaH in the MeCN solvent at 0–23 °C. The ylide **A** was subjected to a one-pot Corey–Chaykovsky reaction with aldehyde **159** to afford epoxide **160** in 98% yield (d.r. = 5:1). Following this, the epoxide mixture in CHCl₃ (chloroform) employing DTAC underwent [3 + 2] cycloaddition, after which the addition of HFIP and HCl at 10 °C without changing the solvent furnished the dihydronaphthalene **162** in 95% yield (r.r. > 20:1). Finally, the reduction *via* LiAlH₄ and the hydrogenation of **162** in EtOAc (ethyl acetate) afforded pycnanthulignene C **163** in 88% overall yield, over four steps (Scheme 23).

Liparacid A **170**,²²⁰ a rare natural product, was isolated from the rhizoma of *Liparis nakaharai* in 2007, and it has relevance in Chinese folk medicine as an anti-tumor agent. In 2020, Song *et al.* reported the first total synthesis of liparacid A **170**, featuring CuI-catalyzed etherification and Corey–Chaykovsky epoxidation as key reactions.²²¹ The synthetic route commenced





Scheme 23 Synthesis of pycnanthulignene C 162.



Scheme 24 Synthesis of liparicid A 170.

with the CuI-catalyzed etherification²²² of 4-bromosalicylaldehyde **164** to furnish a product in 88% yield, and a subsequent Lindlar reduction²²³ gave compound **166** in 97% yield. Following this, compound **166** was subjected to the Corey–Chaykovsky reaction²²⁴ employing dimethyl sulfide and NaOH in *t*BuOH/*H*₂O (9 : 1) solvent to synthesize epoxide **168** (2 steps) in 80% yield. In the next step, the new cascade technique was applied to epoxide **168**, which resulted in the ketone **169** with the desired 2*H*-chromene framework in 45% yield. Ultimately, the three-step sequence, including the Luche reduction²²⁵ of ketone **169** (96% yield), formylation (79% yield), and Kraus–Pinnick oxidation (87% yield), produced the liparicid A **170** in 87% yield (Scheme 24).

4 Conclusion

To summarize, this review presents a detailed overview of the applications of the Corey–Chaykovsky reaction in the total syntheses of various natural products and their analogs. The Corey–Chaykovsky reaction provides an efficient stereoselective route to access cyclopropanes as well as other heterocycles, such as epoxides and aziridines, in high yields under mild conditions. In recent years, this reaction has been consistently proven as a key transformational tool in the toolkit of synthetic organic chemistry, particularly for the synthesis of complex natural products. This review underscores the synthetic utility and stereoselectivity of CC methodology in the synthesis of a diverse



range of natural products, including alkaloids, terpenoids, depsipeptides, polyketides and amino acids. We anticipate that the continued methodological advances in CCR will consolidate it as a reliable and robust technique towards the total synthesis of natural products.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

No primary research results, software or code has been included and no new data were generated or analysed as part of this review.

Acknowledgements

Authors are thankful to the facilities provided by Government College University Faisalabad, Pakistan. A. Irfan extends his appreciation to the Deanship of Research and Graduate Studies at King Khalid University for funding this work through the Large Groups Research Project under grant number (RGP2/172/45). Authors are thankful to the Deanship of Graduate Studies and Scientific Research at the University of Bisha for supporting this work through the Fast-Track Research Support Program.

References

- 1 H. Mayr, B. Kempf and A. R. Ofial, π -Nucleophilicity in carbon-carbon bond-forming reactions, *Acc. Chem. Res.*, 2003, **36**, 66–77.
- 2 A. Mushtaq, A. F. Zahoor, M. N. Ahmad, S. G. Khan, N. Akhter, U. Nazeer, A. Mansha, H. Ahmad, A. R. Chaudhry and A. Irfan, Accessing the synthesis of natural products and their analogues enabled by the Barbier reaction: a review, *RSC Adv.*, 2024, **14**, 33536–33567.
- 3 R. Akhtar, A. F. Zahoor, M. Irfan, T. H. Bokhari and A. ul Haq, Recent green synthetic approaches toward Ullmann reaction: A review, *Chem. Pap.*, 2022, **76**, 7275–7293.
- 4 E. J. Corey and M. Chaykovsky, Dimethyloxosulfonium methylide ((CH₃)₂SOCH₂) and dimethylsulfonium methylide ((CH₃)₂SCH₂). Formation and application to organic synthesis, *J. Am. Chem. Soc.*, 1965, **87**, 1353–1364.
- 5 E. J. Corey and M. Chaykovsky, Methylsulfanylcarbanion, *J. Am. Chem. Soc.*, 1962, **84**, 866–867.
- 6 S. K. Thompson and C. H. Heathcock, Total synthesis of some marasmane and lactarane sesquiterpenes, *J. Org. Chem.*, 1992, **57**, 5979–5989.
- 7 A. H. Li, L. X. Dai and V. K. Aggarwal, Asymmetric ylide reactions: epoxidation, cyclopropanation, aziridination, olefination, and rearrangement, *Chem. Rev.*, 1997, **97**, 2341–2372.
- 8 A. Merz and G. Märkl, Phase-transfer-catalyzed Production of Sulfur Ylides in an Aqueous System, *Angew. Chem., Int. Ed. Engl.*, 1973, **12**, 845–846.
- 9 A. Ciaccio, A. L. Drahus, R. M. Meis, C. T. Tingle, M. Smrtka and R. Geneste, Instant methylide modification of the Corey–Chaykovsky epoxide synthesis, *Synth. Commun.*, 2003, **33**, 2135–2143.
- 10 J. A. Ciaccio and C. E. Aman, Instant methylide, modification of the Corey–Chaykovsky epoxide synthesis, *Synth. Commun.*, 2006, **36**, 1333–1341.
- 11 L. Liu, R. Tian, S. Liu, X. Chen, L. Guo and Y. Che, Pestaloficiols A–E, bioactive cyclopropane derivatives from the plant endophytic fungus *Pestalotiopsis fici*, *Bioinorg. Med. Chem.*, 2008, **16**, 6021–6026.
- 12 M. Watanabe, T. Hirokawa, T. Kobayashi, A. Yoshida, Y. Ito, S. Yamada, N. Orimoto, Y. Yamasaki, M. Arisawa and S. Shuto, Investigation of the bioactive conformation of histamine H3 receptor antagonists by the cyclopropylic strain-based conformational restriction strategy, *J. Med. Chem.*, 2010, **53**, 3585–3593.
- 13 H. K. Zhang, L. F. Yu, J. B. Eaton, P. Whiteaker, O. K. Onajole, T. Hanania, D. Brunner, R. J. Lukas and A. P. Kozikowski, Chemistry, pharmacology, and behavioral studies identify chiral cyclopropanes as selective $\alpha 4\beta 2$ -nicotinic acetylcholine receptor partial agonists exhibiting an antidepressant profile. Part II, *J. Med. Chem.*, 2013, **56**, 5495–5504.
- 14 J. X. Qiao, D. L. Cheney, R. S. Alexander, A. M. Smallwood, S. R. King, K. He, A. R. Rendina, J. M. Luetgen, R. M. Knabb, R. R. Wexler and P. Y. S. Lam, Achieving structural diversity using the perpendicular conformation of alpha-substituted phenylcyclopropanes to mimic the bioactive conformation of ortho-substituted biphenyl P4 moieties: Discovery of novel, highly potent inhibitors of Factor Xa, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4118–4123.
- 15 A. W. Johnson and R. B. LaCount, 9-Dimethylsulfonium fluorenylide, *Chem. Ind.*, 1958, 1440–1441.
- 16 C. R. Johnson, Utilization of sulfoximines and derivatives as reagents for organic synthesis, *Acc. Chem. Res.*, 1973, **6**, 341–347.
- 17 C. R. Johnson and C. W. Schroeck, Chemistry of sulfoxides and related compounds. XLV. Asymmetric syntheses using optically active oxosulfonium alkylides, *J. Am. Chem. Soc.*, 1973, **95**, 7418–7423.
- 18 A. Kazia, R. Melngaile, A. Mishnev and J. Veliks, Johnson–Corey–Chaykovsky fluorocyclopropanation of double activated alkenes: scope and limitations, *Org. Biomol. Chem.*, 2020, **18**, 1384–1388.
- 19 M. A. Shaikh, A. S. Ubale and B. Gnanaprakasam, Amberlyst-A26-Mediated Corey–Chaykovsky Cyclopropanation of 9-Alkylidene-9 H-fluorene under Continuous Process, *J. Org. Chem.*, 2024, **89**, 2283–2293.
- 20 S. S. Malunavar, S. M. Sutar, P. Prabhala, H. M. Savanur, R. G. Kalkhambkar, G. Aridoss and K. K. Laali, Facile synthesis of libraries of functionalized cyclopropanes and oxiranes using ionic liquids—A new approach to the classical Corey–Chaykovsky reaction, *Tetrahedron Lett.*, 2021, **81**, 153339.
- 21 A. Irfan, S. Faiz, A. Rasul, R. Zafar, A. F. Zahoor, K. Kotwica-Mojzzych, M. Mojzzych and M. Exploring, the synergistic



- anticancer potential of benzofuran-oxadiazoles and triazoles: Improved ultrasound-and microwave-assisted synthesis, molecular docking, hemolytic, thrombolytic and anticancer evaluation of furan-based molecules, *Molecules*, 2022, 27, 1023.
- 22 A. Irfan, S. Faisal, A. F. Zahoor, R. Noreen, S. A. Al-Hussain, B. Tuzun, R. Javaid, A. A. Elhenawy, M. E. A. Zaki, S. Ahmad and M. H. Abdellattif, In silico development of novel benzofuran-1, 3, 4-oxadiazoles as lead inhibitors of M. tuberculosis polyketide synthase 13, *Pharmaceuticals*, 2023, 16, 829.
- 23 A. Irfan, S. Faisal, S. Ahmad, S. A. Al-Hussain, S. Javed, A. F. Zahoor, B. Parveen and M. E. Zaki, Structure-based virtual screening of furan-1, 3, 4-oxadiazole tethered N-phenylacetamide derivatives as novel class of hTYR and hTYRP1 inhibitors, *Pharmaceuticals*, 2023, 16, 344.
- 24 C. A. D. Caiuby, L. G. Furniel and A. C. B. Burtoloso, Asymmetric transformations from sulfoxonium ylides, *Chem. Sci.*, 2022, 13, 1192–1209.
- 25 G. D. Bisag, S. Ruggieri, M. Fochi and L. Bernardi, Sulfoxonium ylides: simple compounds with chameleonic reactivity, *Org. Biomol. Chem.*, 2020, 18, 8793–8809.
- 26 T. F. Schneider, J. Kaschel and D. B. Werz, A new golden age for donor-acceptor cyclopropanes, *Angew. Chem., Int. Ed.*, 2014, 53, 5504–5523.
- 27 K. Ghosh and S. Das, Recent advances in ring-opening of donor acceptor cyclopropanes using C-nucleophiles, *Org. Biomol. Chem.*, 2021, 19, 965–982.
- 28 Y. Xia, X. Liu and X. Feng, Asymmetric catalytic reactions of donor-acceptor cyclopropanes, *Angew. Chem., Int. Ed.*, 2021, 60, 9192–9204.
- 29 V. Pirenne, B. Muriel and J. Waser, Catalytic enantioselective ring-opening reactions of cyclopropanes, *Chem. Rev.*, 2021, 121, 227–263.
- 30 U. Nazeer, A. Mushtaq, A. F. Zahoor, F. Hafeez, I. Shahzadi and R. Akhtar, Cloke–Wilson rearrangement: a unique gateway to access five-membered heterocycles, *RSC Adv.*, 2023, 13, 35695–35732.
- 31 T. T. Talele, The Cyclopropyl Fragment is a Versatile Player that Frequently Appears in Preclinical/Clinical Drug Molecules, *J. Med. Chem.*, 2016, 59, 8712–8756.
- 32 A. K. Gupta, M. Bharadwaj, A. Kumar and R. Mehrotra, Spiro-oxindoles as a Promising Class of Small Molecule Inhibitors of p53–MDM2 Interaction Useful in Targeted Cancer Therapy, *Top. Curr. Chem.*, 2017, 375, 3.
- 33 W. Shi, Z. Jiang, H. He, F. Xiao, F. Lin, Y. Sun, L. Hou, L. Shen, L. Han, M. Zeng, K. Lai, Z. Gu, X. Chen, T. Zhao, L. Guo, C. Yang, J. Li and S. Chen, Discovery of 3,3'-Spiro [Azetidene]-2-oxoindoline Derivatives as Fusion Inhibitors for Treatment of RSV Infection, *ACS Med. Chem. Lett.*, 2018, 9, 94–97.
- 34 E. Sansinenea and A. Ortiz, The Chemistry of Cyclopropanes and New Insight in Organocatalyzed Asymmetric Cyclopropanation, *Eur. J. Org. Chem.*, 2022, 2022, e202200210.
- 35 J. J. Li, in *Name Reactions in Heterocyclic Chemistry*, John Wiley & Sons, Inc., Hoboken, NJ, 2005, pp. 2–14.
- 36 A. W. Johnson and R. B. Lacount, The Chemistry of Ylids. VI. Dimethylsulfonium Fluorenylide-A Synthesis of Epoxides, *J. Am. Chem. Soc.*, 1961, 83, 417.
- 37 L. X. Dai, X. L. Hou and Y. G. Zhou, Stereoselective Synthesis of Three-membered Ring Compounds via Ylide Routes, *Pure Appl. Chem.*, 1999, 71, 369.
- 38 V. K. Aggarwal and C. L. Winn, Catalytic, Asymmetric Sulfur Ylide-Mediated Epoxidation of Carbonyl Compounds: Scope, Selectivity, and Applications in Synthesis, *Acc. Chem. Res.*, 2004, 37, 611.
- 39 E. M. McGarrigle, E. L. Myers, O. Illa, M. A. Shaw, S. L. Riches and V. K. Aggarwal, Chalcogenides as Organocatalysts, *Chem. Rev.*, 2007, 107, 5841.
- 40 J. F. Briere and P. Metzner, *Organosulfur Chemistry in Asymmetric Synthesis*, Wiley-VCH, Weinheim, Germany, 2008, vol. 37, p. 321.
- 41 S. Li, P. Li and J. Xu, Retro-Corey-Chaykovsky Epoxidation: Converting Geminal Disubstituted Epoxides to Ketones, *Helv. Chim. Acta*, 2019, 102, e1900164.
- 42 V. K. Aggarwal, A. Thompson, R. V. Jones and M. C. Standen, Novel catalytic and asymmetric process for aziridination mediated by sulfur ylides, *J. Org. Chem.*, 1996, 61, 8368–8369.
- 43 V. K. Aggarwal, E. Alonso, G. Fang, M. Ferrara, G. Hynd and M. Porcelloni, Application of chiral sulfides to catalytic asymmetric aziridination and cyclopropanation with in situ generation of the diazo compound, *Angew. Chem., Int. Ed.*, 2001, 40, 1433–1436.
- 44 M. A. Marsini, J. T. Reeves, J. N. Desrosiers, M. A. Herbage, J. Savoie, Z. Li, K. R. Fandrick, C. A. Sader, B. McKibben, D. A. Gao, J. Cui, N. C. Gonella, H. Lee, X. Wei, F. Roschangar, B. Z. Lu and C. H. Senanayake, Diastereoselective synthesis of α -quaternary aziridine-2-carboxylates via Aza-Corey–Chaykovsky aziridination of *N*-tert-butanesulfinyl ketimino esters, *Org. Lett.*, 2015, 17, 5614–5617.
- 45 A. Mushtaq, A. F. Zahoor, M. Bilal, S. M. Hussain, M. Irfan, R. Akhtar, A. Irfan, K. Kotwica-Mojzycz and M. Mojzycz, Sharpless asymmetric dihydroxylation: an impressive gadget for the synthesis of natural products: a review, *Molecules*, 2023, 28, 2722.
- 46 S. Munawar, A. F. Zahoor, S. M. Hussain, S. Ahmad, A. Mansha, B. Parveen, K. G. Ali and A. Irfan, Steglich esterification: A versatile synthetic approach toward the synthesis of natural products, their analogues/derivatives, *Heliyon*, 2024, 10, DOI: [10.1016/j.heliyon.2023.e23416](https://doi.org/10.1016/j.heliyon.2023.e23416).
- 47 R. Munir, A. F. Zahoor, M. N. Anjum, A. Mansha, A. Irfan, A. R. Chaudhry, A. Irfan, K. Kotwica-Mojzycz, M. Glowacka and M. Mojzycz, Yamaguchi esterification: a key step toward the synthesis of natural products and their analogs—a review, *Front. Chem.*, 2024, 12, 1477764.
- 48 S. Tabassum, A. F. Zahoor, S. Ahmad, R. Noreen, S. G. Khan and H. Ahmad, Cross-coupling reactions towards the synthesis of natural products, *Mol. Diversity*, 2022, 26, 647–689.
- 49 E. J. Corey, Y. Arai and C. Mioskowski, Total synthesis of (+)-5, 6-oxido-7, 9-trans, 11, 14-cis-eicosapentaenoic



- acid, a possible precursor of SRSA, *J. Am. Chem. Soc.*, 1979, **101**, 6748.
- 50 D. G. Farnum, T. Veysoglu, A. M. Cardt, B. Duhl-Emswiler, T. A. Pancoast, T. J. Reitz and R. T. CardE, A stereospecific synthesis of (+)-disparlure, sex attractant of the gypsy moth, *Tetrahedron Lett.*, 1977, **18**, 4009.
- 51 M. Rosenberger and C. Neukom, Total synthesis of (5S, 6R, 7E, 9E, 11Z, 14Z)-5-hydroxy-6-[(2R)-2-amino-2-(carboxyethyl) thio]-7, 9, 11, 14-eicosatetraenoic acid, a potent SRS-A, *J. Am. Chem. Soc.*, 1980, **102**, 5425.
- 52 M. M. Heravi, S. Asadi, N. Nazari and B. Malekzadeh Lashkariani, Developments of Corey-Chaykovsky in organic reactions and total synthesis of natural products, *Curr. Org. Synth.*, 2016, **13**, 308–333.
- 53 E. J. Corey and M. Chaykovsky, Dimethyloxosulfonium Methylide ((CH₃)₂SOCH₂) and Dimethylsulfonium Methylide ((CH₃)₂SCH₂). Formation and Application to Organic Synthesis, *J. Am. Chem. Soc.*, 1965, **87**, 1353–1364.
- 54 A. A. Fadeev, A. S. Makarov, O. A. Ivanova, M. G. Uchuskin and I. V. Trushkov, Extended Corey–Chaykovsky reactions: transformation of 2-hydroxychalcones to benzannulated 2, 8-dioxabicyclo [3.2. 1] octanes and 2, 3-dihydrobenzofurans, *Org. Chem. Front.*, 2022, **9**, 737–744.
- 55 R. O. Shcherbakov, D. A. Myasnikov, I. V. Trushkov and M. G. Uchuskin, Extended Version of the Corey–Chaykovsky Reaction: Synthesis of 2, 4-Substituted Furans by the Treatment of β-Dialkylamino Chalcones with Dimethylsulfonium Methylide, *J. Org. Chem.*, 2023, **88**, 8227–8235.
- 56 B. Singh, A. J. Ansari, N. Malik and S. S. V. Ramasastry, An interrupted Corey–Chaykovsky reaction of designed azaarenium salts: synthesis of complex polycyclic spiro- and fused cyclopropanoids, *Chem. Sci.*, 2023, **14**, 6963–6969.
- 57 Y. Zhou, N. Li, W. Cai and Y. Huang, Asymmetric Sequential Corey–Chaykovsky Cyclopropanation/Cloke–Wilson Rearrangement for the Synthesis of 2, 3-Dihydrofurans, *Org. Lett.*, 2021, **23**, 8755–8760.
- 58 J. P. Maurya and S. S. V. Ramasastry, Interrupted Corey–Chaykovsky Reaction of Tethered Bis-Enones to Access 2, 3-Epoxy-hexahydrofluoren-9-ones, *Org. Lett.*, 2024, **26**, 4571–4575.
- 59 D. J. Bernhardson, S. Lara-Boykin, J. C. McWilliams, Y. Nieves-Quinones, L. S. Sharninghausen, R. A. Singer and Z. C. Girvin, Asymmetric Synthesis of the cis-1, 2-Diaryltetralin Vepdegestrant Core via an Enantioselective Intramolecular Corey-Chaykovsky Epoxidation, *Org. Process Res. Dev.*, 2024, **28**, 4420–4430.
- 60 A. Bendelac, F. Benedetti, V. Doublet-Decabras, R. Lokovi, F. Decalogne and A. Bigot, Fit-for-Purpose Synthesis of an Aza-Cryptophycin Analogue as the Payload for an Antibody–Drug Conjugate, *Org. Process Res. Dev.*, 2022, **26**, 2145–2154.
- 61 K. Vamshikrishna and P. Srihari, Total synthesis of (+)-varitriol and (+)-6'-epi-varitriol, *Tetrahedron*, 2012, **68**, 1540–1546.
- 62 J. S. Yadav, S. Pamu, D. C. Bhunia and S. Pabbaraja, Formal total synthesis of ovalcin by carbohydrate approach, *Synlett*, 2007, **2007**(06), 0992–0994.
- 63 G. A. Guerrero-Vásquez, C. K. Z. Andrade, J. M. Molinillo and F. A. Macías, Practical First Total Synthesis of the Potent Phytotoxic (±)-Naphthotectone, Isolated from *Tectona grandis*, *Eur. J. Org. Chem.*, 2013, **2013**, 6175–6180.
- 64 M. I. Adamovskiy, O. S. Artamonov, A. V. Tymtsunik and O. O. Grygorenko, The synthesis of a 2-azabicyclo [3.1. 0] hexane by rearrangement of a spirocyclic epoxide, *Tetrahedron Lett.*, 2014, **55**, 5970–5972.
- 65 C. Molinaro, D. Gauvreau, G. Hughes, S. Lau, S. Lauzon, R. Angelaud, P. D. O'Shea, J. Janey, M. Palucki, S. R. Hoerrner, C. E. Raab, R. R. Sidler, M. Belley and Y. Han, Remote Electronic Control in the Regioselective Reduction of Succinimides: A Practical, Scalable Synthesis of EP4 Antagonist MF-310, *J. Org. Chem.*, 2009, **74**, 6863–6866.
- 66 G. L. Beutner and D. T. George, Opportunities for the application and advancement of the Corey–Chaykovsky cyclopropanation, *Org. Process Res. Dev.*, 2022, **27**, 10–41.
- 67 E. J. Choi, S. J. Nam, L. Paul, D. Beatty, C. A. Kauffman, P. R. Jensen and W. Fenical, Previously uncultured marine bacteria linked to novel alkaloid production, *Chem. Biol.*, 2015, **22**, 1270–1279.
- 68 J. B. Sweeney, Aziridines: Epoxides' ugly cousins, *Chem. Soc. Rev.*, 2002, **31**, 247–258.
- 69 S. Mandal, S. Bhuyan, S. Jana, J. Hossain, K. Chhetri and B. G. Roy, Efficient visible light mediated synthesis of quinolin 2(1H)-ones from quinoline N-oxides, *Green Chem.*, 2021, **23**, 5049–5055.
- 70 S. O. Simonetti, E. L. Larghi and T. S. Kaufman, The 3,4-dioxygenated 5-hydroxy-4-aryl-quinolin-2(1H)-one alkaloids. Results of 20 years of research, uncovering a new family of natural products, *Nat. Prod. Rep.*, 2016, **33**, 1425–1446.
- 71 A. Buljan, V. Stepanić, A. Čikoš, S. Babić Brčić, K. Bojanić and M. Roje, Total Synthesis and Biological Profiling of Putative (±)-Marinoaziridine B and (±)-N-Methyl Marinoaziridine A, *Mar. Drugs*, 2024, **22**, 310.
- 72 A. Buljan and M. Roje, Application of green chiral chromatography in enantioseparation of newly synthesized racemic marinoepoxides, *Mar. Drugs*, 2022, **20**, 530.
- 73 P. G. Baraldi, R. Budriesi, B. Cacciari, A. Chiarini, L. Garuti, G. Giovanninetti, A. Leoni and M. Roberti, Synthesis and calcium antagonist activity of dialkyl 1,4-dihydro-2,6-dimethyl-4-(nitrogenous heteroaryl)-3,5-pyridine dicarboxylates, *Collect. Czech. Chem. Commun.*, 1992, **57**, 169–178.
- 74 T. Durst, R. N. Ben and M. N. Roy, *e-EROS Encyclopedia of Reagents for Organic Synthesis*, Wiley, New York, NY, USA, 2013, pp. 1–3.
- 75 M. Lounasmaa, P. Hanhinen and M. Westersund, *The Alkaloids: Chemistry and Biology*, ed. G. A. Cordell, Academic Press, San Diego, 1999, vol. 52, pp. 103–195.



- 76 O. A. Nam joshi and J. M. Cook, *The Alkaloids: Chemistry and Biology*, ed. H.-J. Knölker, Academic Press, San Diego, 2016, vol. 76, pp. 63–169.
- 77 S. E. Lewis, I. Alkorta and J. Elguero, Recent advances in the chemistry of macroline, sarpagine and ajmaline-related indole alkaloids, *Tetrahedron*, 2006, **62**, 8655–8681.
- 78 M. T. Rahman, V. V. P. B. Tiruveedhula and J. M. Cook, Synthesis of bisindole alkaloids from the Apocynaceae which contain a macroline or sarpagine unit: a review, *Molecules*, 2016, **21**, 1525.
- 79 S. Rolf, H. J. Bruns, T. Wichter, P. Kirchhof, M. Ribbing, K. Wasmer, M. Paul, G. Breithardt, W. Haverkamp and L. Eckardt, The ajmaline challenge in Brugada syndrome: diagnostic impact, safety, and recommended protocol, *Eur. Heart J.*, 2003, **24**, 1104–1112.
- 80 O. A. Namjoshi and J. M. Cook, Sarpagine and related alkaloids, *Alkaloids*, 2016, **76**, 63–169.
- 81 C. R. Edwankar, R. V. Edwankar, O. A. Namjoshi, X. Liao and J. M. Cook, Stereospecific approach to the synthesis of ring-A oxygenated sarpagine indole alkaloids. Total synthesis of the dimeric indole alkaloid P-(+)-dispegatrine and six other monomeric indole alkaloids, *J. Org. Chem.*, 2013, **78**, 6471–6487.
- 82 D. Ponglux, S. Wongseripipatana, S. Subhadhirasakul, H. Takayama, M. Yokota, K. Ogata, C. Phisalaphong, N. Aimi and S. Sakai, Studies on the indole alkaloids of *Gelsemium elegans* (thailand): Structure elucidation and proposal of biogenetic route, *Tetrahedron*, 1988, **44**, 5075–5094.
- 83 C. Rujjanawate, D. Kanjanapothi and A. Panthong, Pharmacological effect and toxicity of alkaloids from *Gelsemium elegans* Benth, *J. Ethnopharmacol.*, 2003, **89**, 91–95.
- 84 V. Dutt, S. Thakur, V. J. Dhar and A. Sharma, Diazo Insertion based Strategy for the Formation of Hexahydrocyclohepta [b] indoles, *Pharmacogn. Rev.*, 2010, **4**, 185–194.
- 85 G. L. Jin, Y. P. Su, M. Liu, Y. Xu, J. Yang, K. J. Liao and C. X. Yu, Medicinal plants of the genus *Gelsemium* (Gelsemiaceae, Gentianales)-A review of their phytochemistry, pharmacology, toxicology and traditional use, *J. Ethnopharmacol.*, 2014, **152**, 33–52.
- 86 Z. Yang, Q. Tan, Y. Jiang, J. Yang, X. Su, Z. Qiao, W. Zhou, L. He, H. Qiu and M. Zhang, Asymmetric total synthesis of sarpagine and koumine alkaloids, *Angew. Chem.*, 2021, **133**, 13215–13221.
- 87 P. Singh, K. Samanta, S. K. Das and G. Panda, Amino acid chirons: a tool for asymmetric synthesis of heterocycles, *Org. Biomol. Chem.*, 2014, **12**, 6297–6339.
- 88 W. Yuan and S. Ma, Ligand Controlled Highly Selective Copper-Catalyzed Borylcuprations of Allenes with Bis (pinacolato) diboron, *Adv. Synth. Catal.*, 2012, **354**, 1867–1872.
- 89 J. M. Müller, E. Schlittler and H. J. Bein, Reserpin, der sedative Wirkstoff aus *Rauwolfia serpentina* Benth, *Experientia*, 1952, **8**, 338.
- 90 E. Schlittler, P. R. Ulshafer, M. L. Pandow, R. M. Hunt and L. Dorfman, *Rauwolfia* alkaloids, XVI. Deserpidine, a new alkaloid from *Rauwolfia canescens*, *Experientia*, 1955, **11**, 64–65.
- 91 R. Strawbridge, R. R. Javed, J. Cave, S. Jauhar and A. H. Young, The effects of reserpine on depression: A systematic review, *J. Psychopharmacol.*, 2023, **37**, 248–260.
- 92 R. E. Woodson, H. W. Younken, E. Schlitter and J. A. Schneider, *Rauwolfia: Botany, Pharmacognosy, Chemistry and Pharmacology*, Little, Brown and Co., Boston, 1957.
- 93 C. Szántay, G. Blaskó, K. Honty, E. Baitz-Gács, J. Tamás and L. Tóke, Synthesis of reserpine-type alkaloids, III. Synthesis of rac-deserpidine and a rac-raunescine epimer, *Liebigs Ann. Chem.*, 1983, **8**, 1292–1309.
- 94 S. Sakai and M. Ogawa, Chemical Transformation of Reserpine to Deserpidine, *Heterocycles*, 1978, **10**, 67–71.
- 95 O. Miyata, Y. Hirata, T. Naito and I. Ninomiya, A formal total synthesis of (±)-deserpidine, *Heterocycles*, 1984, **22**, 1041–1044.
- 96 P. Wu, Q. Zhou, X. Y. Liu, F. Xue and Y. Qin, Synthetic studies towards (-)-deserpidine: Total synthesis of the stereoisomer and derivative of (-)-deserpidine, *Chin. Chem. Lett.*, 2021, **32**, 401–404.
- 97 P. S. Mariano, E. W. Baxter, D. Labaree and H. L. Ammon, Formal total synthesis of deserpidine demonstrating a versatile amino-Claisen rearrangement/Wenkert cyclization strategy for the preparation of functionalized yohimbane ring systems, *J. Am. Chem. Soc.*, 1990, **112**, 7682–7692.
- 98 G. Varchi, A. Battaglia, C. Samorì, E. Baldelli, B. Danieli, G. Fontana and E. Bombardelli, Synthesis of deserpidine from reserpine, *J. Nat. Prod.*, 2005, **68**, 1629–1631.
- 99 P. Wu, Q. Zhou, X. Y. Liu, F. Xue and Y. Qin, Synthetic studies towards (-)-deserpidine: Total synthesis of the stereoisomer and derivative of (-)-deserpidine, *Chin. Chem. Lett.*, 2021, **32**, 401–404.
- 100 O. H. Oldenzien, D. van Leusen and A. M. VanLeusen, Chemistry of sulfonylmethyl isocyanides. 13. A general one-step synthesis of nitriles from ketones using tosylmethyl isocyanide. Introduction of a one-carbon unit, *J. Org. Chem.*, 1977, **42**, 3114–3118.
- 101 C. Fuganti and S. Serra, Baker's yeast-mediated enantioselective synthesis of the bisabolane sesquiterpenes (+)-curcuphenol, (+)-xanthorrhizol, (-)-curcuquinone and (+)-curcuhydroquinone, *J. Chem. Soc., Perkin Trans.*, 2000, **1**, 3758–3764.
- 102 M. Bellido, C. Riego-Mejías, G. Sciortino, X. Verdager, A. Lledós and A. Riera, Regioselective Ring-Opening of Oxetanes Catalyzed by Lewis Superacid Al (C₆F₅)₃, *Adv. Synth. Catal.*, 2024, **366**, 925–933.
- 103 F. Menges and A. Pfaltz, Threonine-derived phosphinite-oxazoline ligands for the Ir-catalyzed enantioselective hydrogenation, *Adv. Synth. Catal.*, 2002, **344**, 40–44.
- 104 K. Okuma, Y. Tanaka, S. Kaji and H. Ohta, Reaction of dimethyloxosulfonium methylide with epoxides. Preparation of oxetanes, *J. Org. Chem.*, 1983, **48**, 5133–5134.



- 105 V. K. Honwad and A. S. Rao, Terpenoids-LXIX: Absolute Configuration of (–) α -Curcumene, *Tetrahedron*, 1965, **21**, 2593–2604.
- 106 G. S. da Silva, P. Pozzatti, F. Rigatti, R. Hörner, S. H. Alves, C. A. Mallmann and B. M. Heinzmann, Antimicrobial evaluation of sesquiterpene α -curcumene and its synergism with imipenem, *J. Microbiol., Biotechnol. Food Sci.*, 2015, **4**, 434–436.
- 107 N. K. Utkina, A. E. Makarchenko, O. V. Shchelokova and M. V. Virovaya, Antioxidant Activity of Phenolic Metabolites from Marine Sponges, *Chem. Nat. Compd.*, 2004, **40**, 373–377.
- 108 G. N. Santos da Silva, P. Pozzatti, F. Rigatti, R. Hörner, S. H. Alves, C. A. Mallmann and B. M. Heinzmann, Antimicrobial Evaluation of Sesquiterpene α -Curcumene and Its Synergism with Imipenem, *J. Microbiol., Biotechnol. Food Sci.*, 2015, **4**, 434–436.
- 109 H. Itokawa, F. Hirayama, K. Funakoshi and K. Takeya, Studies on the Antitumor Bisabolane Sesquiterpenoids Isolated from Curcuma Xanthorrhiza, *Chem. Pharm. Bull.*, 1985, **33**, 3488–3492.
- 110 M. Bellido, C. Riego-Mejías, A. Diaz-Moreno, X. Verdaguer and A. Riera, Enantioselective Ir-catalyzed hydrogenation of terminal homoallyl Sulfones: total synthesis of (–)-curcumene, *Org. Lett.*, 2023, **25**, 1453–1457.
- 111 K. Okuma, Y. Tanaka, S. Kaji and H. Ohta, Reaction of dimethyloxosulfonium methylide with epoxides. Preparation of oxetanes, *J. Org. Chem.*, 1983, **48**, 5133–5134.
- 112 A. Cabre, S. Rafael, G. Sciortino, G. Ujaque, X. Verdaguer, A. Lledos and A. Riera, Catalytic Regioselective Isomerization of 2,2 Disubstituted Oxetanes to Homoallylic Alcohols, *Angew. Chem., Int. Ed.*, 2020, **59**, 7521–7527.
- 113 A. Pfaltz, J. Blankenstein, R. Hilgraf, E. Hörmann, S. McIntyre, F. Menges, M. Schönleber, S. P. Smidt, B. Wustenberg and N. Zimmermann, Iridium-Catalyzed Enantioselective Hydrogenation of Olefins, *Adv. Synth. Catal.*, 2003, **345**, 33–43.
- 114 B. K. Peters, T. Zhou, J. Rujirawanich, A. Cadu, T. Singh, W. Rabten, S. Kerdphon and P. G. Andersson, An Enantioselective Approach to the Preparation of Chiral Sulfones by Ir-Catalyzed Asymmetric Hydrogenation, *J. Am. Chem. Soc.*, 2014, **136**, 16557–16562.
- 115 J. Mazuela, P. O. Norrby, P. G. Andersson, O. Pámies and M. Diéguez, Pyranoside Phosphite-Oxazoline Ligands for the Highly Versatile and Enantioselective Ir-Catalyzed Hydrogenation of Minimally Functionalized Olefins. A Combined Theoretical and Experimental Study, *J. Am. Chem. Soc.*, 2011, **133**, 13634–13645.
- 116 S. Serra, Preparation and Use of Enantioenriched 2-Aryl Propylsulfonylbenzene Derivatives as Valuable Building Blocks for the Enantioselective Synthesis of Bisabolane Sesquiterpenes, *Tetrahedron: Asymmetry*, 2014, **25**, 1561–1572.
- 117 R. O. Hutchins and K. Learn, Regio- and Stereoselective Reductive Replacement of Allylic Oxygen, Sulfur, and Selenium Functional Groups by Hydride via Catalytic Activation by Palladium (0) Complexes, *J. Org. Chem.*, 1982, **47**, 4380–4382.
- 118 G. Stakanovs, A. Blazevisa, S. Belyakov, D. Rasina and A. Jirgensons, Semisynthesis of Linariophyllenes A–C and Rumphellolide H, Structure Revisions and Proposed Biosynthesis Pathways, *J. Nat. Prod.*, 2023, **86**, 2368–2378.
- 119 G. Stakanovs, A. Mishnev, D. Rasina and A. J. Jirgensons, A concise bioinspired semisynthesis of rumphellaones A–C and their C-8 epimers from β -caryophyllene, *J. Nat. Prod.*, 2020, **83**, 2004–2009.
- 120 G. Stakanovs, S. Belyakov, A. Jirgensons and D. Rasina, Convergent biomimetic semisynthesis of disesquiterpenoid rumphellolide, *Org. Biomol. Chem.*, 2022, **20**, 2455–2461.
- 121 A. Maliori, T. Athanasiadou, V. Psomiadou, G. G. Bagkavou and C. I. Stathakis, Syntheses of ent-Aquilanol A and ent-Aquilanol B via Retro-Cycloisomerization of (–)-Caryophyllene Oxide. Access to Medium-Sized Oxygenated Carbocyclic Scaffolds, *Org. Lett.*, 2022, **24**, 6242–6246.
- 122 L. D. Syntrivanis, I. Némethová, D. Schmid, S. Levi, A. Prescimone, F. Bissegger, D. T. Major and K. J. Tiefenbacher, Four-step access to the sesquiterpene natural product presilphiperfolan-1 β -ol and unnatural derivatives via supramolecular catalysis, *J. Am. Chem. Soc.*, 2020, **142**, 5894–5900.
- 123 C. Y. Bemis, C. N. Ungarean, A. S. Shved, C. S. Jamieson, T. Hwang, K. S. Lee, K. N. Houk and D. J. Sarlah, Total synthesis and computational investigations of sesquiterpene-tropolones ameliorate stereochemical inconsistencies and resolve an ambiguous biosynthetic relationship, *J. Am. Chem. Soc.*, 2021, **143**, 6006–6017.
- 124 W. Parker, R. A. Raphael and J. S. Roberts, Neoclovene a novel rearrangement product of caryophyllene, *Tetrahedron Lett.*, 1965, **6**, 2313–2316.
- 125 I. C. Nigam and L. Levi, Essential Oils and Their Constituents. XXVI. 1 Rearrangement of Caryophyllene Oxide during Gas Chromatography, *J. Org. Chem.*, 1965, **30**, 653–654.
- 126 Y. Yamada, S. Arima, T. Nagamitsu, K. Johmoto, H. Uekusa, T. Eguchi, K. Shin-ya, D. E. Cane and H. Ikeda, Novel terpenes generated by heterologous expression of bacterial terpene synthase genes in an engineered *Streptomyces* host, *J. Antibiot.*, 2015, **68**, 385–394.
- 127 J. Liu, Y. Zhou and Z. X. Yu, Six-Step Total Synthesis of Isohirsut-4-ene through [5+ 2+ 1] Cycloaddition and Transannular Epoxide–Alkene Cyclization, *Org. Lett.*, 2022, **24**, 1444–1447.
- 128 A. G. Kutateladze and D. M. Kuznetsov, Triquinanes and Related Sesquiterpenes Revisited Computationally: Structure Corrections of Hirsutanols B and D, Hirsutenol E, Cucumin B, Antrodins C–E, Chondroterpenes A and H, Chondrosterins C and E, Dichrocephone A, and Pethybrene, *J. Org. Chem.*, 2017, **82**, 10795–10802.
- 129 N. Nguyen and D. J. Tantillo, Using quantum chemical computations of NMR chemical shifts to assign relative



- configurations of terpenes from an engineered *Streptomyces* host, *J. Antibiot.*, 2016, **69**, 534.
- 130 Y. Wang, J. Wang, J. Su, F. Huang, L. Jiao, Y. Liang, D. Yang, S. Zhang, P. A. Wender and Z. X. Yu, A Computationally Designed Rh(I)-Catalyzed Two-Component [5 + 2+1] Cycloaddition of Ene-vinylcyclopropanes and CO for the Synthesis of Cyclooctenones, *J. Am. Chem. Soc.*, 2007, **129**, 10060–10061.
- 131 Y. Wang and Z. X. Yu, Rhodium-Catalyzed [5 + 2 + 1] Cycloaddition of Ene-Vinylcyclopropanes and CO: Reaction Design, Development, Application in Natural Product Synthesis, and Inspiration for Developing New Reactions for Synthesis of Eight Membered Carbocycles, *Acc. Chem. Res.*, 2015, **48**, 2288–2296.
- 132 Y. Wang, W. Liao, Y. Wang, L. Jiao and Z. X. Yu, Mechanism and Stereochemistry of Rhodium-Catalyzed [5+2+1] Cycloaddition of Ene-Vinylcyclopropanes and Carbon Monoxide Revealed by Visual Kinetic Analysis and Quantum Chemical Calculations, *J. Am. Chem. Soc.*, 2022, **144**, 2624–2636.
- 133 P. A. Wender and T. J. Williams, [(arene)Rh(cod)]⁺ Complexes as Catalysts for [5 + 2] Cycloaddition Reactions, *Angew. Chem., Int. Ed.*, 2002, **41**, 4550–4553.
- 134 P. A. Wender, J. A. Love and T. J. Williams, Rhodium-Catalyzed [5 + 2] Cycloaddition Reactions in Water, *Synlett*, 2003, **2003**, 1295–1298.
- 135 J. Liu, Y. Zhou, J. Zhu and Z. X. Yu, Synthesizing Molecules with Linear Tricyclic 5/5/5 and 6/5/5 Skeletons via [5 + 2 + 1]/Ene Strategy, *Org. Lett.*, 2021, **23**, 7566–7570.
- 136 K. D. Wellington, R. C. Cambie, P. S. Rutledge and P. R. J. Bergquist, Chemistry of Sponges. 19. Novel Bioactive Metabolites from *Hamigera tarangaensis*, *J. Nat. Prod.*, 2000, **63**, 79–85.
- 137 R. C. Cambie, C. E. F. Rickard, P. S. Rutledge and K. D. Wellington, K. D. Hamigerin A and a hamigerin D decomposition product, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 2001, **57**, 958–960.
- 138 J. D. Dattelbaum, A. J. Singh, J. J. Field, J. H. Miller and P. T. J. Northcote, The nitrogenous hamigerans: Unusual amino acid-derivatized aromatic diterpenoid metabolites from the New Zealand marine sponge *Hamigera tarangaensis*, *Org. Chem.*, 2015, **80**, 304–312.
- 139 A. J. Singh, J. D. Dattelbaum, J. J. Field, Z. Smart, E. F. Woolly, J. M. Barber, R. Heathcott, J. H. Miller and P. T. Northcote, structurally diverse hamigerans from the New Zealand marine sponge *Hamigera tarangaensis*: NMR-directed isolation, structure elucidation and antifungal activity, *Org. Biomol. Chem.*, 2013, **11**, 8041–8051.
- 140 E. F. Woolly, A. J. Singh, E. R. Russell, J. H. Miller and P. T. J. Northcote, Hamigerans R and S: nitrogenous diterpenoids from the New Zealand marine sponge *Hamigera tarangaensis*, *J. Nat. Prod.*, 2018, **81**, 387–393.
- 141 X. Li, D. Xue, C. Wang and S. Gao, Total Synthesis of the Hamigerans, *Angew. Chem.*, 2016, **128**, 10096–10100.
- 142 D. C. Duquette, T. Jensen and B. M. Stoltz, Progress towards the total synthesis of hamigerans C and D: a direct approach to an elaborated 6-7-5 carbocyclic core, *J. Antibiot.*, 2018, **71**, 263–267.
- 143 B. Jiang and M. Dai, Synthetic Studies toward the Hamigerans with a 6–7–5 Tricyclic Core, *Org. Lett.*, 2020, **22**, 4176–4179.
- 144 C. Borger, A. W. Schmidt and H. Knolker, H. First Total Synthesis of Murrastifoline B and an Improved Route to Murrastifoline F, *Synlett*, 2014, **25**, 1381–1384.
- 145 W. Hao, J. H. Harenberg, X. Wu, S. N. MacMillan and S. Lin, Diastereo- and enantioselective formal [3+ 2] cycloaddition of cyclopropyl ketones and alkenes via Ti-catalyzed radical redox relay, *J. Am. Chem. Soc.*, 2018, **140**, 3514–3517.
- 146 Y. H. Hsu, A. Hirota, S. Shima, M. Nakagawa, H. Nozaki, T. Tada and M. Nakayama, Structure of Myrocin C, a New Diterpene Antibiotic Produced by a Strain of *Myrothecium* Sp, *Agric. Biol. Chem.*, 1987, **51**, 3455–3457.
- 147 M. Nakagawa, Y. H. Hsu, A. Hirota, S. Shima, M. Nakayama and C. Myrocin, a New Diterpene Antitumor Antibiotic from *Myrothecium Verrucaria*. I. Taxonomy of the Producing Strain, Fermentation, Isolation and Biological Properties, *J. Antibiot.*, 1989, **42**, 218–222.
- 148 Y. H. Hsu, M. Nakagawa, A. Hirota, S. Shima and M. Nakayama, Structure of Myrocin B, a New Diterpene Antibiotic Produced by *Myrothecium Verrucaria*, *Agric. Biol. Chem.*, 1988, **52**, 1305–1307.
- 149 N. A. Lehr, A. Meffert, L. Antelo, O. Sterner, H. Anke and R. W. S. Weber, Antiamoebins, Myrocin B and the Basis of Antifungal Antibiosis in the Coprophilous Fungus *Stilbella Erythrocephala* (Syn. *S. Fimetaria*), *FEMS Microbiol. Ecol.*, 2006, **55**, 105–112.
- 150 M. Tsukada, M. Fukai, K. Miki, T. Shiraishi, T. Suzuki, K. Nishio, T. Sugita, M. Ishino, K. Kinoshita, K. Takahashi, M. Shiro and K. Koyama, Chemical Constituents of a Marine Fungus, *Arthrinium Sacchari*, *J. Nat. Prod.*, 2011, **74**, 1645–1649.
- 151 C. Klemke, S. Kehraus, A. D. Wright and G. M. König, New Secondary Metabolites from the Marine Endophytic Fungus *Apiospora Montagnei*, *J. Nat. Prod.*, 2004, **67**, 1058–1063.
- 152 S. S. Ebada, B. Schulz, V. Wray, F. Totzke, M. H. G. Kubbutat, W. E. G. Müller, A. Hamacher, M. U. Kassack, W. Lin and P. Proksch, Arthrinins A–D: Novel Diterpenoids and Further Constituents from the Sponge Derived Fungus *Arthrinium* Sp, *Bioorg. Med. Chem.*, 2011, **19**, 4644–4651.
- 153 W. Wei, J. Gao, Y. Shen, Y. L. Chu, Q. Xu and R. X. Tan, Immunosuppressive Diterpenes from *Phomopsis* sp. S12, *Eur. J. Org. Chem.*, 2014, **2014**, 5728–5734.
- 154 M. Y. Chu-Moyer and S. J. Danishefsky, A Remarkable Cyclopropanation: The Total Synthesis of Myrocin C, *J. Am. Chem. Soc.*, 1992, **114**, 8333–8334.
- 155 M. Y. Chu-Moyer, S. J. Danishefsky and G. K. Schulte, Total Synthesis of (±)-Myrocin C, *J. Am. Chem. Soc.*, 1994, **116**, 11213–11218.
- 156 H. E. Simmons and R. D. Smith, A New Synthesis of Cyclopropanes from Olefins, *J. Am. Chem. Soc.*, 1958, **80**, 5323–5324.



- 157 M. Y. Chu-Moyer and S. J. Danishefsky, On the Mode of Action of Myrocin C: Evidence for a CC-1065 Connection, *Tetrahedron Lett.*, 1993, **34**, 3025–3028.
- 158 N. Zander, W. Langschwager and H. M. R. Hoffmann, The Enol Lactone Approach to Protected Hydroxy γ -Lactones (5-Hydroxy-dihydro-furan-2-ones), *Synth. Commun.*, 1996, **26**, 4577–4590.
- 159 W. Langschwager and H. M. R. Hoffmann, Ring-Chain Tautomerism Provides a Route to 7a-hydroxy-3a-methyl-2,7-dioxo perhydrobenzofuran. Synthesis of the Hydroxy γ -Lactone Substructure of Myrocin and Other Bioactive Natural Products, *Liebigs Ann.*, 1995, **1995**, 797–802.
- 160 C. Economou, M. Tomanik and S. B. Herzon, Synthesis of Myrocin G, the Putative Active Form of the Myrocin Antitumor Antibiotics, *J. Am. Chem. Soc.*, 2018, **140**, 16058–16061.
- 161 M. Tomanik, C. Economou, M. C. Frischling, M. Xue, V. A. Marks, B. Q. Mercado and S. B. Herzon, Development of a convergent enantioselective synthetic route to (–)-myrocin G, *J. Org. Chem.*, 2020, **85**, 8952–8989.
- 162 C. Xu, L. Zhang and S. Luo, Asymmetric Enamine Catalysis with β -Ketoesters by Chiral Primary Amine: Divergent Stereocontrol Modes, *J. Org. Chem.*, 2014, **79**, 11517–11526.
- 163 T. K. Au, W. S. H. Chick and P. C. Leung, The biology of ophiobolins, *Life Sci.*, 2000, **67**, 733–742.
- 164 M. Rowley, M. Tsukamoto and Y. Kishi, Total synthesis of (+)-ophiobolin C, *J. Am. Chem. Soc.*, 1989, **111**, 2735.
- 165 K. Tsuna, N. Noguchi and M. Nakada, Convergent total synthesis of (+)-ophiobolin A, *Angew. Chem., Int. Ed.*, 2011, **50**, 9452–9455.
- 166 K. Tsuna, N. Noguchi and M. Nakada, Enantioselective Total Synthesis of (+)-Ophiobolin A, *Chem.–Eur. J.*, 2013, **19**, 5476–5486.
- 167 Z. G. Brill, H. K. Grover and T. J. Maimone, Enantioselective synthesis of an ophiobolin sesterterpene via a programmed radical cascade, *Science*, 2016, **352**, 1078–1082.
- 168 D. Q. Thach, Z. G. Brill, H. K. Grover, K. V. Esguerra, J. K. Thompson and T. J. Maimone, Total synthesis of (+)-6-epi-ophiobolin A, *Angew. Chem., Int. Ed.*, 2020, **59**, 1532–1536.
- 169 A. B. Charette, H. Juteau, H. Lebel and C. Molinaro, Enantioselective cyclopropanation of allylic alcohols with dioxaborolane ligands: scope and synthetic applications, *J. Am. Chem. Soc.*, 1998, **120**, 11943–11952.
- 170 A. B. Charette and J. Naud, Regioselective opening of substituted (cyclopropylmethyl) lithiums derived from cyclopropylmethyl iodides, *Tetrahedron Lett.*, 1998, **39**, 7259–7262.
- 171 T. Mukaiyama, J. I. Matsuo and H. Kitagawa, A new and one-pot synthesis of α , β -unsaturated ketones by dehydrogenation of various ketones with *N*-tert-butyl phenylsulfinimidoyl chloride, *Chem. Lett.*, 2000, **29**, 1250–1251.
- 172 C. E. Cook, L. P. Whichard, B. Turner, M. E. Wall and G. H. Egley, Germination of witchweed (*Striga lutea* Lour.): Isolation and properties of a potent stimulant, *Science*, 1966, **154**, 1189–1190.
- 173 K. Akiyama, K. Matsuzaki and H. Hayashi, Plant sesquiterpenes induce hyphal branching in arbuscular mycorrhizal fungi, *Nature*, 2005, **435**, 824–827.
- 174 A. Besserer, V. Puech-Pagès, P. Kiefer, V. Gomez-Roldan, A. Jauneau, S. Roy, J. C. Portais, C. Roux, G. Bécard and N. Séjalon-Delmas, Strigolactones stimulate arbuscular mycorrhizal fungi by activating mitochondria, *PLoS Biol.*, 2006, **4**, e226, DOI: [10.1371/journal.pbio.0040226](https://doi.org/10.1371/journal.pbio.0040226).
- 175 K. Yoneyama, X. Xie, K. Yoneyama, T. Kisugi, T. Nomura, Y. Nakatani, K. Akiyama and C. S. P. McErlean, Which are the major players, canonical or non-canonical strigolactones, *J. Exp. Bot.*, 2018, **69**, 2231–2239.
- 176 N. Mori, A. Sado, X. Xie, K. Yoneyama, K. Asami, Y. Seto, T. Nomura, S. Yamaguchi, K. Yoneyama and K. Akiyama, Chemical identification of 18-hydroxycaractonoic acid as an LjMAX1 product and in planta conversion of its methyl ester to canonical and non-canonical strigolactones in *Lotus japonicus*, *Phytochemistry*, 2020, **174**, 112349.
- 177 K. Wolkenstein, H. Sun, H. Falk and C. Griesinger, Structure and absolute configuration of Jurassic polyketide-derived spiroborate pigments obtained from microgram quantities, *J. Am. Chem. Soc.*, 2015, **137**, 13460–13463.
- 178 K. Wolkenstein, J. H. Gross and H. Falk, Boron-containing organic pigments from a Jurassic red alga, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 19374–19378.
- 179 G. Shabuer, K. Ishida, S. J. Pidot, M. Roth, H. M. Dahse and C. Hertweck, Plant pathogenic anaerobic bacteria use aromatic polyketides to access aerobic territory, *Science*, 2015, **350**, 670–674.
- 180 S. Pidot, K. Ishida, M. Cyrulies and C. Hertweck, Discovery of clostrubin, an exceptional polyphenolic polyketide antibiotic from a strictly anaerobic bacterium, *Angew. Chem., Int. Ed.*, 2014, **126**, 7990–7993.
- 181 K. Kirita, H. Matsumoto, G. Endo and S. Hosokawa, Total Syntheses of Borolithochromes A, D and G, *Angew. Chem., Int. Ed.*, 2024, **63**, e202400586.
- 182 M. Kobayashi, S. Aoki, N. Ohyabu, M. Kurosu, W. Wang and I. Kitagawa, Arenastatin A, a potent cytotoxic depsipeptide from the Okinawan marine sponge *Dysidea arenaria*, *Tetrahedron Lett.*, 1994, **35**, 7969–7972.
- 183 S. N. Rao, R. A. MoreO'Ferrall, S. C. Kelly, D. R. Boyd and R. Agarwall, Acid-catalyzed aromatizations of arene oxides and arene hydrates: are arene oxides homoaromatic?, *J. Am. Chem. Soc.*, 1993, **115**, 5458–5465.
- 184 K. Kirita, H. Matsumoto, G. Endo, K. Inoue and S. Hosokawa, Total syntheses of borolithochromes H1, H2, I1, and I2, *Biosci., Biotechnol., Biochem.*, 2024, **88**, 1144–1154.
- 185 P. L. Anelli, C. Biffi, F. Montanari and S. Quici, Fast and selective oxidation of primary alcohols to aldehydes or to carboxylic acids and of secondary alcohols to ketones mediated by oxoammonium salts under two-phase conditions, *J. Org. Chem.*, 1987, **52**, 2559–2562.
- 186 P. Lupattelli, M. D'Auria, N. D. Blasio and F. Lenti, A novel approach to combretastatins: from trans-epoxide to CA-4



- and its dioxolane derivative, *Eur. J. Org. Chem.*, 2009, **2009**, 141–145.
- 187 S. N. Rao, R. A. More O'Ferrall, S. C. Kelly, D. R. Boyd and R. Agarwal, Acid-catalyzed aromatizations of arene oxides and arene hydrates: are arene oxides homoaromatic?, *J. Am. Chem. Soc.*, 1993, **115**, 5458–5465.
- 188 A. M. Bernard, M. R. Ghiani, P. P. Piras and A. Rivoldini, Dealkylation of activated alkyl aryl ethers using lithium chloride in dimethylformamide, *Synthesis*, 1989, **1989**, 287–79.
- 189 I. T. Harrison, Cleavage of alkyl aryl ethers with lithium iodide, *J. Chem. Soc. Chem. Commun.*, 1969, **11**, 616a.
- 190 M. Kobayashi, M. Kurosu, N. Ohyabu, W. Wang, S. Fujii and I. Kitagawa, The absolute stereostructure of arenastatin A, a potent cytotoxic depsipeptide from the Okinawan Marine sponge *Dysidea arenaria*, *Chem. Pharm. Bull.*, 1994, **42**, 2196–2198.
- 191 M. Kobayashi, M. Kurosu, W. Wang and I. Kitagawa, A total synthesis of arenastatin A, an extremely potent cytotoxic depsipeptide, from the Okinawan marine sponge *Dysidea arenaria*, *Chem. Pharm. Bull.*, 1994, **42**, 2394–2396.
- 192 G. Trimurtulu, I. Ohtani, G. M. L. Patterson, R. E. Moore, T. H. Corbett, F. A. Valeriote and L. Demchik, Total Structures of Cryptophycins, Potent Antitumor Depsipeptides from the Blue-Green Alga *Nostoc* sp. Strain GSV 224, *J. Am. Chem. Soc.*, 1994, **116**, 4729–4737.
- 193 V. K. Aggarwal, J. Charmant, L. Dudin, M. Porcelloni and J. Richardson, Effect of sulfide structure on enantioselectivity in catalytic asymmetric epoxidation of aldehydes: Mechanistic insights and implications, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5467–5471.
- 194 Y. Mihara, H. Kadoya, S. Kakihana and N. Kotoku, Concise and Stereospecific Total Synthesis of Arenastatin A and Its Segment B Analogs, *Molecules*, 2024, **29**, 4058.
- 195 D. W. Hoard, E. D. Moher, M. J. Martinelli and B. H. Norman, Synthesis of Cryptophycin 52 Using the Shi Epoxidation, *Org. Lett.*, 2002, **4**, 1813–1815.
- 196 P. Kumar, N. Kaur, R. Kumar and P. Banerjee, α , β -Unsaturated Carbonyls for One-Pot Transition-Metal-Free Access to 3, 6-Dihydro-2 H-pyrans, *J. Org. Chem.*, 2022, **87**, 7167–7178.
- 197 M. Guldbandt, T. N. Johansen, K. Frydenvang, H. Brauner-Osborne, T. B. Stensbol, B. Nielsen, R. Karla, F. Santi, P. Krogsgaard-Larsen and U. Madsen, Glutamate receptor ligands: synthesis, stereochemistry, and enantiopharmacology of methylated 2- amino adipic acid analogs, *Chirality*, 2002, **14**, 351–363.
- 198 M. Staudt, N. Liu, F. Malhaire, Y. Doroudian, L. Prézeau, E. Renard, Z. Hasanpour, J.-P. Pin and L. Bunch, Synthesis and pharmacological characterization of conformationally restricted 2-amino-Adipic acid analogs and carboxycyclopropyl glycines as selective metabotropic glutamate 2 receptor agonists, *Eur. J. Med. Chem.*, 2024, **266**, 116157.
- 199 J. Zhang, Z. W. Liu, Y. L. Ao, L. J. Hu, C. J. Wei, Q. H. Zhang, M. F. Yuan, Y. Wang, Q. W. Zhang, W. C. Ye and X. Q. Zhang, Hunterines A–C, three unusual monoterpene indole alkaloids from *Hunteria zeylanica*, *J. Org. Chem.*, 2019, **84**, 14892–14897.
- 200 Y. Zhang, X. Ding, S. Shao, L. L. Guo, Q. Zhao, X. J. Hao and H. P. He, Melocochines A and B, two alkaloids from the fruits of *Melodinus cochinchinensis*, *Org. Lett.*, 2019, **21**, 9272–9275.
- 201 M. Kitajima, M. Nakazawa, Y. Wu, N. Kogure, R. P. Zhang and H. Takayama, Kopsiyunnanines L and M, Strychnos-related monoterpene indole alkaloids from Yunnan *Kopsia arborea*, *Tetrahedron*, 2016, **72**, 6692–6696.
- 202 A. Chiaroni, L. Randriambola, C. Riche and H. P. Husson, Structure of goniomine, an alkaloid of a new type biogenetically related to indole alkaloids. X-ray analysis of dihydrogoniomine, *J. Am. Chem. Soc.*, 1980, **102**, 5920–5921.
- 203 B. Zsigulics, P. Angyal, B. B. Mészáros, J. Daru, S. Varga and T. Soós, Bioinspired Synthesis of (–)-Hunterine A: Deciphering the Key Step in the Biogenetic Pathway, *Chem.–Eur. J.*, 2025, **31**, e202404501.
- 204 L. Kürti and B. Czako, *Strategic Applications of Named Reactions in Organic Synthesis: Background and Detailed Mechanisms*, Elsevier, 2005, pp. 102–103.
- 205 T. Saito, T. Suzuki, K. Takeuchi, T. Matsumoto and K. Suzuki, Implication and improvement of stereoselective methylenation of a chiral aldehyde related to total synthesis of the furaquinocins, *Tetrahedron Lett.*, 1997, **38**, 3755–3758.
- 206 F. Bohlmann and P. Singh, A guaiane-5, 12-olide from *Hypochoeris cretensis*, *Phytochemistry*, 1982, **21**, 2119–2120.
- 207 S. Huang, C. A. Pettaway, H. Uehara, C. D. Bucana and I. J. Fidler, Blockade of NF- κ B activity in human prostate cancer cells is associated with suppression of angiogenesis, invasion, and metastasis, *Oncogene*, 2001, **20**, 4188–4197.
- 208 S. Mirzaei, S. Saghari, F. Bassiri, R. Raesi, A. Zarrabi, K. Hushmandi, G. Sethi and V. Tergaonkar, NF- κ B as a regulator of cancer metastasis and therapy response: A focus on epithelial–mesenchymal transition, *J. Cell. Physiol.*, 2022, **237**, 2770–2795.
- 209 C. Zidorn, H. Stuppner, M. Tiefenthaler and G. Konwalinka, Cytotoxic activities of Hypocretenolides from *Leontodon hispidus*, *J. Nat. Prod.*, 1999, **62**, 984–987.
- 210 C. Zidorn, V. M. Dirsch, P. Rüngeler, S. Sosa, R. D. Loggia, I. Merfort, H. L. Pahl, A. M. Vollmar and H. Stuppner, Anti-inflammatory activities of hypocretenolides from *Leontodon hispidus*, *Planta Med.*, 1999, **65**, 704–708.
- 211 B. Chen, X. Zhang, Y. Yang, D. Xu, Q. Wu, S. Wang, S. Bao, X. Zhang, Y. Ding, L. Wang and Y. Chen, Hypocretenolides: collective total syntheses and activities toward metastatic colon cancer, *Chem. Sci.*, 2024, **15**, 6397–6401.
- 212 M. L. de Faria, R. D. A. Magalhaes, F. C. Silva, L. G. D. O. Matias, M. A. Ceschi, U. Brocksom and T. J. Brocksom, Enantiodivergent syntheses of cycloheptenone intermediates for guaiane sesquiterpenes, *Tetrahedron: Asymmetry*, 2000, **11**, 4093–4103.
- 213 T. Ohashi, Y. Miyazawa, S. Ishizaki, Y. Kurobayashi and T. Saito, Identification of odor-active trace compounds in



- blooming flower of damask rose (*Rosa damascena*), *J. Agric. Food Chem.*, 2019, **67**, 7410–7415.
- 214 Y. Miyazawa, K. Kawaguchi, R. Katsuta, T. Nukada and K. Ishigami, Analog synthesis of DAMASCENOLIDE™, an important aroma component of roses, and their odor properties, *Biosci., Biotechnol., Biochem.*, 2020, **84**, 1560–1569.
- 215 Y. Miyazawa, K. Kawaguchi, R. Katsuta, T. Nukada and K. Ishigami, Studies on analogs of DAMASCENOLIDETM: Part 3. Synthesis and odor evaluation of dimethylated, cyclopropanated, and other analogs of DAMASCENOLIDE™, *Biosci., Biotechnol., Biochem.*, 2021, **85**, 756–764.
- 216 R. B. Teponno, S. Kusaria and M. Spittler, Recent Advances in Research on Lignans and Neolignans, *Nat. Prod. Rep.*, 2016, **33**, 1044–1092.
- 217 E. Alfonzo and A. B. Beeler, A Sterically Encumbered Photoredox Catalyst Enables the Unified Synthesis of the Classical Lignan Family of Natural Products, *Chem. Sci.*, 2019, **10**, 7746–7754.
- 218 E. Alfonzo, A. M. Millimaci and A. B. Beeler, Photoredox Generated Carbonyl Ylides Enable a Modular Approach to Aryltetralin, Dihydronaphthalene, and Arylnaphthalene Lignans, *Org. Lett.*, 2020, **22**, 6489–6493.
- 219 E. C. N. Nono, P. Mkounga, V. Kuete, K. Marat, P. G. Hultin and A. E. Nkengfack, Pycnanthulignenes A–D, Antimicrobial Cyclolignene Derivatives from the Roots of *Pycnanthus Angolensis*, *J. Nat. Prod.*, 2010, **73**, 213–216.
- 220 W. L. Kuo, Y. L. Huang, C. C. Shen, B. J. Shieh and C. C. Chen, Prenylated Benzoic Acids and Phenanthrenes from *Liparis nakaharai*, *J. Chin. Chem. Soc.*, 2007, **54**, 1359–1362.
- 221 L. Song, Q. Su, X. Lin, Z. Du, H. Xu, M. A. Ouyang, H. Yao, R. Tong and R. Cascade, Claisen and Meinwald Rearrangement for One-Pot Divergent Synthesis of Benzofurans and 2 H-Chromenes, *Org. Lett.*, 2020, **22**, 3004–3009.
- 222 D. Bell, M. R. Davies, G. R. Geen and I. S. Mann, Copper(I) Iodide: A Catalyst for the Improved Synthesis of Aryl Propargyl Ethers, *Synthesis*, 1995, 707–712.
- 223 X. Wang, N. Lu, Q. Yang, D. Gong, C. Lin, S. Zhang, M. Xi, Y. Gao, L. Wei, Q. Guo and Q. You, Studies on chemical modification and biology of a natural product, gambogic acid (III): Determination of the essential pharmacophore for biological activity, *Eur. J. Med. Chem.*, 2011, **46**, 1280–1290.
- 224 S. Parisotto and A. Deagostino, Synthesis of High Functionalized Allyl Alcohols from Vinyl Oxiranes and *N*-Tosylhydrazones via a Tsuji-Trost-Like "Palladium-Iodide" Catalyzed Coupling, *Org. Lett.*, 2018, **20**, 6891–6895.
- 225 A. L. Gemal and J. L. Luche, Lanthanoids in organic synthesis. 6. Reduction of α -enones by sodium borohydride in the presence of lanthanoid chlorides: synthetic and mechanistic aspects, *J. Am. Chem. Soc.*, 1981, **103**, 5454–5459.

